Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-01-15-D-270 Vandetanib

Stand: Februar 2017

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

Vandetanib (neues AWG) [Medulläres Schilddrüsenkarzinom bei Jugendlichen und Kindern im Alter von 5 Jahren und älter]	
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 Anlage II
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	Es liegen keine Beschlüsse vor.
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:	
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). (Zulassung vom 16.12.2016)

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation medulläres Schilddrüsenkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 24.01.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, 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.

Die Recherche ergab 295 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 4 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung des medullären Schilddrüsenkarzinoms (MTC) bei Patienten im Kindes- und Jugendalter ab 5 Jahren mit nicht resektabler, lokal fortgeschrittener oder metastasierter Erkrankung.

Abkürzungen:

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
EBRT	External beam radiotherapy
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IMRT	Intensity-modulated radiation therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MTC	Medulläres Schilddrüsenkarzinom
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
RECIST	Response Evaluation Criteria in Solid Tumor
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

Cochrane Reviews

Keine identifiziert.

Systematische Reviews

Keine identifiziert.

Leitlinien

National Comprehensive Cancer Network (NCCN), 2016 [1]. NCCN clinical practice guidelines in oncology: Thyroid carcinoma. Version 1.2016	**Zielsetzung** Recommendations for the prevention, diagnosis, and management of malignancies across the continuum of care. <u>Patientenpopulation:</u> Erwachsene und Kinder mit Schilddrüsenkrebs *Hinweis zum Kapitel Diskussion:* „Discussion Update in Progress“
	Methodik ***Grundlage der Leitlinie**:* Update der vorherigen Leitlinie. Systematische Literatursuche. Interdisziplinäres Team mit Patientenvertretung. Strukturierter Konsensusprozess. ***Suchzeitraum*:** Oktober 2013 bis Oktober 2014 ***LoE/GoR**:* **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 noted.** ***Weitere Kriterien für die Qualität einer Leitlinie:*** • Jährliche Updates bzw. Reviews geplant • Conflict of Interest: offengelegt und online einsehbar
	Empfehlungen *Hinweise der FB Med:* • Die Empfehlungen wurden in den Entscheidungspfaden der Leitlinie nicht differenziert für Kinder und Erwachsene dargestellt. Im Text wurde teils auf die Alterspopulation eingegangen. • Die dargestellten Empfehlungen sind nur teils mit Quellen im jeweili-

gen Hintergrundtext hinterlegt.

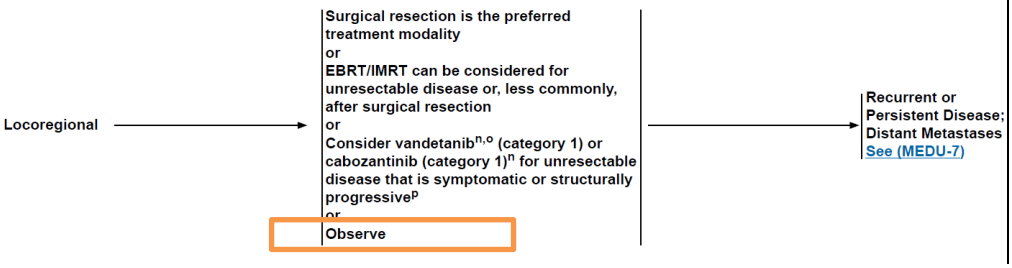
- Die relevanten Therapien sind optisch in den Entscheidungspfaden hervorgehoben.

Hinweis:

All recommendations are category 2A unless otherwise indicated.

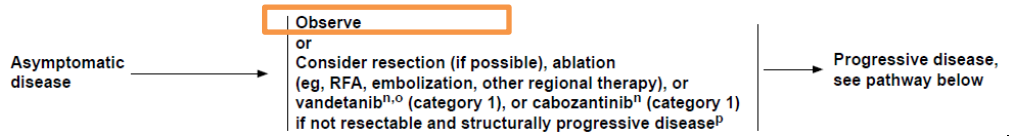
Medullary Carcinoma: Recurrent or persistant disease

Locoregional



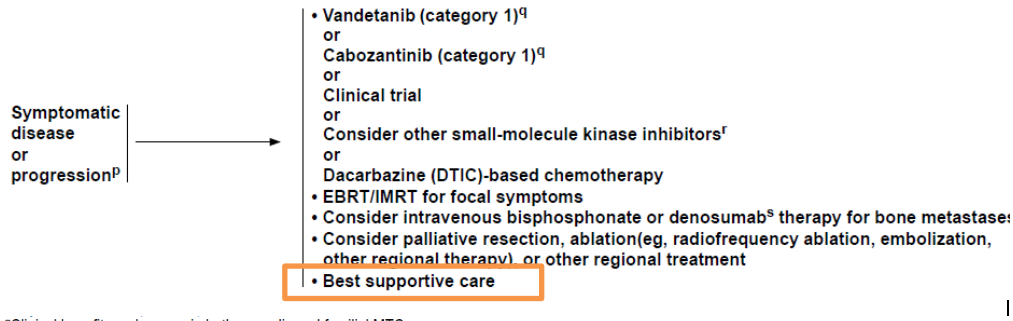
[n]Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[o]Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted dist program, will be able to prescribe and dispense the drug.
[p]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).

Distant metastases - asymptotic disease



[n]Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[o]Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribu program, will be able to prescribe and dispense the drug.
[p]Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in A Thyroid Carcinoma (THYR-B).

Distant metastases - symptomatic disease or progression



[q]Clinical benefit can be seen in both sporadic and familial MTC.
[r]While not FDA approved for treatment of medullary thyroid cancer, other commercially available small-molecule kinase inhibitors (such as sorafenib, sunitinib, pazopanib) can be considered if clinical trials, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabo
[s]Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are a increased risk.

	When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended with (or without) postoperative EBRT or IMRT. For unresectable locoregional disease that is symptomatic or structurally progressive, the following options can be considered: 1) EBRT or IMRT; 2) vandetanib (category 1); or 3) cabozantinib (category 1). Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include: 1) palliative resection, ablation (eg, radiofrequency, embolization), or other regional treatment; 2) vandetanib (category 1); or 3) cabozantinib (category 1) (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but observation is acceptable given the lack of data regarding alteration in outcome. In the setting of symptomatic disease or progression, the NCCN Panel recommends the following: 1) vandetanib (category 1);[347,452,456] 2) cabozantinib (category 1);[349] 3) clinical trial; or 4) consider other small molecule kinase inhibitors (ie, sorafenib, sunitinib, pazopanib) if clinical trials, vandetanib, or cabozantinib are not available or appropriate.[331,457-462] If the patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.[403,463-465] EBRT or IMRT can be used for focal symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.[386-388] Best supportive care is also recommended. 347. Wells SA, Jr., Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134-141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22025146. 348. Traynor K. Cabozantinib approved for advanced medullary thyroid cancer. Am J Health Syst Pharm 2013;70:88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23292257. 349. Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639-3646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24002501. 403. Wells SA, Jr., Asa SL, Dralle H, et al. Revised american thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25810047. 452. Robinson BG, Paz-Ares L, Krebs A, et al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab 2010;95:2664-2671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20371662. 456. Wells SA, Jr., Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010;28:767-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20065189. 462. Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. J Clin Endocrinol Metab 2009;94:1493-1499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19258410. 463. Orlandi F, Caraci P, Berruti A, et al. Chemotherapy with dacarbazine and 5-fluorouracil in advanced medullary thyroid cancer. Ann Oncol 1994;5:763-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7826911. 464. Nocera M, Baudin E, Pellegriti G, et al. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs a Calcitonine (GETC). Br J Cancer 2000;83:715-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10952773. 465. Schlumberger M, Abdelmoumene N, Delisle MJ, Couette JE. Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. The Groupe d'Etude des Tumeurs a Calcitonine (GETC). Br J Cancer 1995;71:363-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7530987.
Wells SA et al., 2015 [4]. **American Thyroid Association** Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma	**Zielsetzung** To revise the original Medullary Thyroid Carcinoma: Management Guidelines of the American Thyroid Association. The revised guidelines are focused primarily on the diagnosis and treatment of patients with sporadic medullary thyroid carcinoma (MTC) and hereditary MTC. Patientenpopulation: Erwachsene und Kinder mit medullärem Schilddrüsenkarzinom
	Methodik ***Grundlage der Leitlinie***: Überarbeitung der vorherigen Leitlinie. Systematische Literatursuche und nicht-strukturierter Konsensusprozesse eines interdisziplinären Teams (endocrinology, ethics, genetics, molecular biology, medical oncology, pathology, pediatrics, nuclear medicine, radiation oncology, and surgery) ***Suchzeitraum*:** Januar 1980 bis April 2014

***LoE/GoR**:*

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.

Weitere Kriterien für die Qualität einer Leitlinie:

- Conflict of Interest: offengelegt, aber nicht dargestellt
- Quellen zum Teil im jeweiligen Hintergrundtext zu den Empfehlungen zitiert.

Empfehlungen

Hinweise der FB Med:

- Empfehlungen wurden in der Leitlinie nur teils differenziert für Kinder und Erwachsene dargestellt. Bei den dargestellten Empfehlungen wird die betroffene Altersgruppe nicht beschrieben.
- Die dargestellten Empfehlungen betreffen überwiegend die Behandlung der Metastasen.
- Die dargestellten Empfehlungen sind nur teils mit Quellen im jeweiligen Hintergrundtext hinterlegt.

MANAGEMENT OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC MTC

Hinweis der FB Med: Die dargestellten Empfehlungen enthalten vermutlich nur nicht relevante Behandlungen.

- In the presence of extensive regional or metastatic disease less aggressive surgery in the central and lateral neck may be appropriate to preserve speech, swallowing, parathyroid function, and shoulder mobility. External beam radiotherapy (EBRT), systemic medical therapy, and other nonsurgical therapies should be considered to achieve local tumor control. **Grade C Recommendation**

	In most patients with MTC the goal is to perform a total thyroidectomy, with or without compartment-oriented lymph node dissections. However, in the presence of advanced disease the goals of surgery are more palliative with attention to minimizing complications. In the presence of MTC that invades the trachea, thyroid cartilage, or esophagus, the extent of extirpative surgery (palliative debulking, laryngectomy, esophagectomy, or laryngopharyngectomy) is determined by an assessment of the ability to maintain speech and swallowing and the patient's life expectancy based on the extent of disease and other medical comorbidities. These decisions are best made on an individualized basis by an experienced multidisciplinary medical team, including the patient. **DIAGNOSIS AND TREATMENT OF PATIENTS WITH CLINICALLY EVIDENT METASTATIC DISEASE** *Hinweis der FB Med*: Die dargestellten Empfehlungen enthalten vermutlich nur nicht relevante Behandlungen. • Palliative therapy, including surgery, EBRT, or systemic therapy, should be considered in patients with metastases causing pain, mechanical compression, or signs and symptoms of hormonal excess. **Grade C Recommendation** Palliative surgery can be effective treatment for patients with metastatic disease. The metastases are frequently painful and resistant to medical treatment. Also, space-occupying metastases that cause acute spinal cord compression, or airway and esophageal obstruction (with coughing, dyspnea, and difficulty swallowing) can be improved by resection of tumor, EBRT, or the administration of systemic therapy. Tumor debulking is often effective in alleviating the diarrheal syndrome occurring in patients with advanced MTC.
Perros P et al., 2014 [2]. **British Thyroid Association** Guidelines for the management of thyroid cancer	**Zielsetzung** To provide guidance for all those involved in the management of patients with differentiated thyroid cancer (DTC) and some of the rarer thyroid cancers. Patientenpopulation: Focus of the document is the management of thyroid cancer in adult patients, although childhood thyroid cancer is included briefly in Chapter 15 and Chapter 17 on medullary thyroid cancer.
	Methodik ***Grundlage der Leitlinie****:* Dritte Überarbeitung einer Leitlinie. Systematische Übersichtsarbeit und nicht-strukturierter Konsensusprozesse mit einem interdisziplinären Team (representatives of professional and patient-led organisations) ***Suchzeitraum*:** 2006 bis 2012 ***LoE/GoR****:* nach SIGN

Levels of evidence

1	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Good practice points

Important practical points for which there is not, nor is there likely to be, any research evidence are shown in the guidelines as Good Practice Points, and are marked with a tick box ☑.

Weitere Kriterien für die Qualität einer Leitlinie:

- Conflict of Interest: offengelegt und dargestellt
- Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert.

Empfehlungen

Hinweise der FB Med:

- Die Empfehlungen wurden in der Leitlinie nur teils differenziert für Kinder und Erwachsene dargestellt. Bei den dargestellten Empfehlungen wird nicht auf die betroffene Altersgruppe eingegangen.
- Die dargestellten Empfehlungen betreffen überwiegend die Behandlung der Metastasen.

Medullary thyroid cancer: Treatment of persistent or recurrent disease

Radiotherapy and chemotherapy.

- Routine use of radiolabelled molecules cannot be recommended but entry into trials should be considered. Treatment with unlabelled somatostatin analogues may help control severe diarrhoea from metastatic disease **(4, D)**

Palliative radiotherapy can play a valuable role in unresectable masses and painful bone metastases (Chapters 10.3 and 12.7).

Hinweis der FB Med: Hier wird auf zwei Kapitel zum differenzierten Schilddrüsenkarzinomen verwiesen. Da diese Kapitel sich auf Erwachsene fokussieren, werden diese Verweise nicht dargestellt.

<table>
<tr><td></td><td><u>Palliative care</u>

• Symptomatic distant metastases may respond to surgery, EBRT, thermoablation and chemoembolization (4, D).</td></tr>
<tr><td rowspan="2">Schlumberger M et al., 2012 [3].
European Thyroid Association

2012 European Thyroid Association Guidelines for Metastatic Medullary Thyroid Cancer</td><td>Zielsetzung
Recommendations focus on MTC patients with distant metastases and a detailed follow-up protocol of patients with biochemical or imaging evidence of disease, selection criteria for treatment, and treatment modalities, including local and systemic

This document does not address end-of-life discussions or palliative care.

<u>Patientenpopulation</u>:

• Patients with biochemical or imaging evidence of metastatic disease
• Keine Angabe zur betroffenen Altersgruppe</td></tr>
<tr><td>Methodik
Grundlage der Leitlinie:
Systematische Literatursuche und nicht-strukturierter Konsensusprozesse eines interdisziplinären Teams (clinical expertise, scholarly approach and representation of endocrinology, nuclear medicine, oncology and surgery)

Suchzeitraum: bis Dezember 2011

LoE/GoR:
<table>
<tr><th>Grading type</th><th>Definition</th></tr>
<tr><td colspan="2">Strength of the recommendation</td></tr>
<tr><td>Grade 1</td><td>Strong recommendation (for or against)
Applies to most patients in most circumstances
Benefits clearly outweigh the risk (or vice versa)</td></tr>
<tr><td>Grade 2</td><td>Weak recommendation (for or against)
Best action may differ depending on circumstances or patient values
Benefits and risks or burdens are closely balanced, or uncertain</td></tr>
<tr><td colspan="2">Quality of the evidence</td></tr>
<tr><td>+++</td><td>High quality; evidence at low risk of bias, such as randomized trials showing consistent results directly applicable to the recommendation</td></tr>
<tr><td>++</td><td>Moderate quality; studies with methodological flaws, showing inconsistent or indirect evidence</td></tr>
<tr><td>+</td><td>Low quality; case series or unsystematic clinical observations</td></tr>
</table>

Weitere Kriterien für die Qualität einer Leitlinie:
• Conflict of Interest: offengelegt, aber nicht dargestellt
• Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert.</td></tr>
</table>

Empfehlungen

Hinweise der FB Med:

- Empfehlungen wurden in der Leitlinie ohne Nennung einer Altersgruppe dargestellt.

Systemic Treatment: Chemotherapy and Clinical Trials

- In patients with significant tumor burden and symptomatic or progressive disease according to RECIST, the use of standard chemotherapeutic agents should not be considered as first-line therapy for patients with persistent or recurrent MTC. **Grade: QOE = ++; SOR = grade 2.**

Among cytotoxic drugs, the most frequently used tested agent in MTC patients is doxorubicin, used either alone or in combination with cisplatinum. Response rates ranged from 0 to 22%, with all responses being partial and only lasting a few months [44, 45]. As MTC is a well-differentiated endocrine tumor, various combinations of 5′-fluorouracil, dacarbazine, streptozocin, cyclophosphamide and vincristine have been used, leading to response rates of approximately 20%, with symptomatic improvement in a limited number of patients [46–51].

44 Shimaoka K, Schoenfeld DA, DeWys WD, Creech RH, DeConti R: A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985;56:2155–2160.

45 Williams SD, Birch R, Einhorn LH: Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. Cancer Treat Rep 1986;70:405–407.

46 Orlandi F, Caraci P, Berruti A, Puligheddu B, Pivano G, Dogliotti L, Angeli A: Chemotherapy with dacarbazine and 5-fluorouracil in advanced medullary thyroid cancer. Ann Oncol 1994;5:763–765.

47 Wu LT, Averbuch SD, Ball DW, de Bustros A, Baylin SB, McGuire WP 3rd: Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. Cancer 1994;73:432–436.

48 Schlumberger M, Abdelmoumene N, Delisle MJ, Couette JE: Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. The Groupe d'Etude des Tumeurs a Calcitonine (GETC). Br J Cancer 1995;71:363–365.

49 Bajetta E, Rimassa L, Carnaghi C, Seregni E, Ferrari L, Di Bartolomeo M, Regalia E, Cassata A, Procopio G, Mariani L: 5-Fluorouracil, dacarbazine, and epirubicin in the treatment of patients with neuroendocrine tumors. Cancer 1998;83:372–378.

50 Petursson SR: Metastatic medullary thyroid carcinoma. Complete response to combination chemotherapy with dacarbazine and 5-fluorouracil. Cancer 1988;62:1899–1903.

51 Nocera M, Baudin E, Pellegriti G, Cailleux AF, Mechelany-Corone C, Schlumberger M: Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs à Calcitonine (GETC). Br J Cancer 2000;83:715–718.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 23.01.2017

#	Suchfrage
1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
2	MeSH descriptor: [Carcinoma, Medullary] explode all trees
3	thyroid:ti,ab,kw or medullary:ti,ab,kw or C-cell*:ti,ab,kw (Word variations have been searched)
4	tumor*:ti,ab,kw or tumour*:ti,ab,kw or carcinoma*:ti,ab,kw or neoplas*:ti,ab,kw or cancer*:ti,ab,kw (Word variations have been searched)
5	"MTC":ti,ab,kw (Word variations have been searched)
6	#3 and #4
7	#1 or #2 or #5 or #6
8	#7 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 23.01.2017

#	Suchfrage
1	Thyroid Neoplasms[MeSH Terms]
2	carcinoma, medullary[MeSH Terms]
3	Thyroid cancer, medullary[Supplementary Concept]
4	Familial medullary thyroid carcinoma[Supplementary Concept]
5	thyroid[Title/Abstract]
6	(medullary[Title/Abstract]) OR C-cell*[Title/Abstract]
7	((((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR cancer*[Title/Abstract])
8	(#1) AND #6
9	((#5) AND #6) AND #7
10	((((#2) OR #3) OR #4) OR #8) OR #9
11	(#10) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
12	(#11) AND ("2012/01/01"[PDAT] : "2017/01/23"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 23.01.2017

#	Suchfrage
1	Thyroid Neoplasms[MeSH Terms]

2	carcinoma, medullary[MeSH Terms]
3	Thyroid cancer, medullary[Supplementary Concept]
4	Familial medullary thyroid carcinoma[Supplementary Concept]
5	((thyroid[Title/Abstract]) OR medullary[Title/Abstract]) OR c-cell*[Title/Abstract]
6	(((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR cancer*[Title/Abstract]) OR neoplas*[Title/Abstract]
7	#5 AND (#6)
8	(#1 OR #2 OR #3 OR #4 OR #7)
9	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
10	#8 AND (#9)
11	(#10) AND ("2012/01/01"[PDAT] : "2017/01/23"[PDAT])

Literatur:

1. **National Comprehensive Cancer Network (NCCN).** NCCN clinical practice guidelines in oncology: Thyroid carcinoma. Version 1.2016 [online]. Fort Washington (USA): NCCN; 2016. [Zugriff: 23.01.2017]. URL: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.

2. **Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard GE, et al.** Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014;81 Suppl 1:1-122.

3. **Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JW.** 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. Eur Thyroid J 2012;1(1):5-14.

4. **Wells SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al.** Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25(6):567-610.