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-B-154 Sonidegib

Stand: September 2017

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

Sonidegib
[zur Behandlung des lokal fortgeschrittenen Basalzellkarzinoms]

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.	Operation Strahlentherapie Kryotherapie Kürettage, alleine oder in Kombination mit Elektrodesikkation Elektrodesikkation Lasertherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach §35a SGB V: - Vismodegib - Beschluss vom 04.08.2016
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:	
Sonidegib L01XX48 Odomzo®	<u>Zugelassenes Anwendungsgebiet:</u> Odomzo ist angezeigt für die Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem Basalzellkarzinom (BCC), die für eine kurative Operation oder eine Strahlentherapie nicht in Frage kommen.
5-Fluorouracil topisch L01BC02 Efudix® 5% Creme	Als Behandlungsversuch kann Efudix statt der vorzuziehenden chirugischen Therapie auch zur Behandlung oberflächlicher Basaliome angewendet werden, wenn chirurgische oder radiologische Maßnahmen erfolglos waren oder nicht anwendbar sind, z. B. bei multiplen Läsionen oder an Stellen, die schwierig zu behandeln sind. Die Diagnose sollte vor der Behandlung histologisch abgesichert werden, da Efudix sich bei anderen Arten von Basaliomen nicht als ausreichend wirksam erwiesen hat. Weiterhin ist zu beachten, dass unter dem oberflächlich geheilten Hautareal der Tumor persistieren kann.
Imiquimod D06BB10 Aldara® 5% Creme	Imiquimod-Creme ist bestimmt für die topische Behandlung von: […] Kleinen superfiziellen Basalzellkarzinomen (sBCC) bei Erwachsenen […]
Methylaminolevulinat L01XD03 Metvix®	Nur zur Behandlung von oberflächlichen und/oder nodulären Basaliomen, für deren Behandlung andere verfügbare Therapien aufgrund der möglichen Morbidität im Zusammenhang mit der Behandlung und der geringen kosmetischen Ergebnisse nicht geeignet scheinen, wie etwa Läsionen im mittleren Gesichtsbereich oder an den Ohren, Läsionen auf schwer sonnengeschädigter Haut, bei großflächigen Läsionen oder rezidivierenden Läsionen.
Vismodegib L01XX43 Erivedge®	Erivedge wird angewendet bei erwachsenen Patienten mit: • symptomatischem metastasiertem Basalzellkarzinom • lokal fortgeschrittenem Basalzellkarzinom, bei denen eine Operation oder Strahlentherapie nicht geeignet ist (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2017-B-154 (Sonidegib)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	11.09.2017

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 evidenzbasierten systematischen Leitlinien zur Indikation *Basalzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 08.08.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten 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 279 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 9 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem Basalzellkarzinom (BCC), die für eine kurative Operation oder eine Strahlentherapie nicht in Frage kommen

Abkürzungen:

5-FU	5-fluorouracil
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BCC	basal cell carcinoma
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
EMBASE	Excerpta Medica Database
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HPI	Hedgehog pathway inhibitors
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
laBCC	Locally advanced basal cell carcinoma
mBCC	Metastatic basal cell carcinoma
nBCC	Nodular basal cell carcinoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PDT	photodynamic therapy
QOE	quality of evidence
SE	surgical excision
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2016 [2]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vismodegib vom 4. August 2016 Vgl. auch IQWiG, 2016 [3,4].	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 12. Juli 2013):** Erivedge wird angewendet bei erwachsenen Patienten mit: • symptomatischem metastasiertem Basalzellkarzinom • lokal fortgeschrittenem Basalzellkarzinom, bei denen eine Operation oder Strahlentherapie nicht geeignet ist (siehe Abschnitt 5.1 der Fachinformation). **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** <u>a) Erwachsene Patienten mit symptomatischem metastasiertem Basalzellkarzinom</u> **Zweckmäßige Vergleichstherapie:** Best-Supportive-Care, ggf. unter Einbeziehung einer Operation oder Strahlentherapie Als „Best-Supportive-Care“ (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:** Ein Zusatznutzen ist nicht belegt. <u>b) Erwachsene Patienten mit lokal fortgeschrittenem Basalzellkarzinom, für die weder eine Operation noch eine Strahlentherapie geeignet ist.</u> **Zweckmäßige Vergleichstherapie:** Best-Supportive-Care Als „Best-Supportive-Care“ (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:** Anhaltspunkt für einen geringen Zusatznutzen.

Cochrane Reviews

Es konnten keine relevanten Quellen identifiziert werden.

Systematische Reviews

Jacobsen AA et al., 2016 [5]. Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma: A Systematic Review and Pooled Analysis of Interventional Studies	1. Fragestellung To evaluate clinical experience with HPIs, including efficacy and adverse effects.
	2. Methodik Population: Patienten mit lokal fortgeschrittenem oder metastasierenden Basalzellkarzinom, einschließlich Patienten mit basal-cell nevus syndrome (Gorlin-Syndrome) Intervention: Vismodegib Komparator: keine Vergleiche angegeben Endpunkt: clinical or histological clearance rates, recurrence rates, adverse effects. Suchzeitraum: Bis November 2015 (Suche in PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and EMBASE) Anzahl eingeschlossene Studien: 11 eingeschlossenen Studien, davon 1 randomized placebo-controlled trial,[3] 2 phase 1 clinical trials,[2,7] 2 open-label trials,[6,8] 1 prospective cohort study,[12] 3 prospective case series,[14-16] and 2 retrospective medical record reviews.[17,18] Qualitätsbewertung der Studien: Qualität wurde ohne etablierte Checkliste bewertet (methods of patient recruitment, overall study design, consistency and guidelines used in reporting outcomes) Zusätzlich: Quality Rating Scheme for Studies and Other Evidence: 1, properly powered and conducted randomized clinical trial, systematic review with meta-analysis; 2, well-designed controlled trial without randomization; prospective comparative cohort trial; 3, case-control studies, retrospective cohort study; 4, case series with or without intervention, cross-sectional study; 5, opinion of respected authorities, case reports.
	3. Ergebnisdarstellung Qualitätsbewertung: • 4 studies (36%) were assessed to be of good reporting value; 5

(45%), intermediate; and 2 (18%), poor.

- Quality Rating Scheme for Studies and Other Evidence:
  1 Studie: Kategorie 1, 5 Studien Kategorie 2, 5 Studien Kategorie 4

Efficacy: 8 Studien mit 704 klinisch evaluierbaren Patienten (lokal fortgeschrittenes oder metastatierendes Basalzellkarzinom)
Efficacy für lokal fortgeschrittenen Basalzellkarzinom:

- Response: weighted mean = 64.7% (95% CI, 63.7%-65.6%); range 28.0% to 100%
- complete response: weighted mean = 31.1% (95% CI, 30.4%-31.8%); range: 0.0% to 54.1%
- partial response: weighted mean = 33.6% (95% CI, 33.1%-34.0%); range: 25.5% to 66.7%
- Disease remained stable: weighted mean = 27.2% (95% CI, 26.4%-27.9%); range 0.0% to 48.2%
- Disease progressed: weighted mean = 3.1% (95% CI, 2.7%-3.4%); range: 0.0% to 28.6%

Unerwünschte Ereignisse: 9 Studien mit 803 Patienten (lokal fortgeschrittenes oder metastatierendes Basalzellkarzinom), keine Unterscheidung nach Subtyp vorgenommen

- serious adverse effects: weighted mean = 21.4% (95% CI, 20.9%-21.9%), range: 0.0%to 38.5%
- proportion of patients discontinuing vismodegib due to adverse effects: weighted mean = 28.2% (95% CI, 27.3%-29.1%); range: 0.0% to 53.8%
- Muscle spasms: weighted mean = 66.4% (95% CI, 65.8%-67.0%); range: 20.0% to 100%
- Dysguesia: weighted mean = 57.3% (95% CI, 56.7%-58.0%); range 20.0% to 75.0%
- Weight loss: weighted mean = 33.4% (95%CI, 32.7% to 34.2%); range: 16.0% to 83.3%
- Fatigue: weighted mean = 20.1% (95%CI, 19.5%-20.7%); range: 7.7% to 40.4%
- Alopecia: weighted mean = 61.1%(95%CI,60.8%-61.4%); range: 20.0% to 75.0%
- New-onset squamous cell carcinoma: weighted mean = 1.3% (95%CI, 1.2%-1.5%); range: 0.8% to 20.0%
- Amenorrhea: weighted mean = 32.9% (95% CI, 32.1%-33.6%); range: 27.6% to 100%

Table 4. Summary of Recommendations[21] for HPI Use

Indication	Recommendation	Grade of Recommendation[a]	Quality of Evidence[b]	Selected References
HPI for laBCC	Strong recommendation	1	A	Basset-Seguin et al[8] Chang et al[6] Migden et al[20] Sekulic et al[12]

Abbreviations: CPK, creatine phosphokinase; HPI, Hedgehog pathway inhibitors; laBCC, locally advanced basal cell carcinoma; LFTs, liver function tests; mBCC, metastatic basal cell carcinoma.

[a] Grade of recommendation based on Robinson et al[32] where 1 indicates strong recommendation with high-quality, patient-oriented evidence; 2A, weak recommendation with limited-quality, patient-oriented evidence; and 2B, weak recommendation with low-quality evidence.

[b] Quality of evidence based on Robinson et al[21] where A indicates a systematic review and/or meta-analysis, randomized clinical trials with consistent findings, and/or all-or-none observational study; B, systematic review and/or meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings, and/or lower-quality clinical trial, cohort study, or case-control study; and C, consensus guidelines, usual practice, expert opinion, and/or case series.

[c] CPK monitoring is required by the FDA for sonidegib but not vismodegib.[9,33]

Referenzen:
2. Von HoffDD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma.N Engl J Med. 2009;361(12): 1164-1172.
3. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012;366(23):2180-2188.
6. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib. J AmAcad Dermatol. 2014;70(1):60-69.
7. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced ormetastatic solid tumors. Clin Cancer

	Res. 2011;17(8):2502-2511. 8. Basset-SeguinN, Hauschild A, Grob JJ, et al. Vismodegib in patientswith advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. Lancet Oncol. 2015;16(6):729-736. 12. Sekulic A, MigdenMR, Lewis K, et al; ERIVANCE BCC investigators. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. J AmAcad Dermatol. 2015;72(6):1021-6.e8. 14. Simone PSJ, Strasswimmer J. Four year experience of vismodegib hedgehog inhibitor therapy. J Am Acad Dermatol. In press. 15. Viscusi KS, Hanke CW. Vismodegib for locally advanced basal cell carcinoma: descriptive analysis of a case series and comparison to the literature. J Drugs Dermatol. 2015;14(9):956-962. 16. Gill HS, Moscato EE, Chang AL, Soon S, Silkiss RZ. Vismodegib for periocular and orbital basal cell carcinoma. JAMAOphthalmol. 2013;131(12):1591-1594. 17. Ozgur OK, Yin V, Chou E, et al. Hedgehog pathway inhibition for locally advanced periocular basal cell carcinoma and basal cell nevus syndrome. AmJ Ophthalmol. 2015;160(2):220-227.e2. 18. Demirci H,Worden F, Nelson CC, Elner VM, KahanaA. Efficacy of vismodegib (erivedge) for basal cell carcinoma involving the orbit and periocular area.Ophthal PlastReconstr Surg.2015;31(6):463-466. 20. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. Lancet Oncol. 2015;16(6): 716-728.
	4. Fazit der Autoren Hedgehog pathway inhibitors are an effective, well-tolerated therapy for laBCC and mBCCand have great potential to improve quality of life for many patients who have limited treatment options. 5. *Anmerkung FBMed:* *Interessenkonflikte des Letztautors vorhanden* *Obwohl mindestens eine Studie Vergleiche mit einer Kontrollgruppe enthielten, wurden diese nicht betrachtet. Es wird lediglich die Ansprechrate in der Interventionsgruppe angegeben. Aufgrund der gezeigten Daten erscheinen Schlussfolgerung und Empfehlungen nicht gerechtfertigt.*
Zou Y et al., 2016 [9]. Photodynamic therapy versus surgical excision to basal cell carcinoma: meta-analysis	1. Fragestellung: to evaluate the efficacy of topical photodynamic therapy (PDT) versus surgical excision (SE) for the treatment for nodular basal cell carcinoma (nBCC) by a meta-analysis.
	2. Methodik Population: patients with nodular basal cell carcinoma (nBCC) (Most tumors were within 10 mm (range 5–30 mm).) Intervention: PDT Komparator: SE Endpunkt: complete response rate, cumulative probability of recurrence Suchzeitraum (Aktualität der Recherche) PubMed (January 1946 to October 2015), EMBASE (January 1989 to October 2015), the Cochrane Library (January 1993 to October 2015), China National Knowledge Infrastructure (CNKI) (1999 to October 2015), and VIP (1989 to October 2015).

	Anzahl eingeschlossene Studien = 5 / Patienten 596 Qualitätsbewertung der Studien: Jadad: 5-point scale to assess randomization (0–2 points), double blinding (0–2 points), and withdrawals and dropouts (0–1 point); Cochrane Reviewers' Handbook 5.1.0 about the quality of RCTs (randomization, blinding, withdrawal and loss, allocation concealment, and intentional Analysis – A: adequate, B: unclear, C: inadequate, and D: not used) The I^2 index and Q test were used to test for heterogeneity between study results.
	3. Ergebnisdarstellung **Table 2** Quality assessment based on the Cochrane Collaboration's tool and Jadad rating scale for assessing risk of bias in included studies Study (year) | Random sequence generation | Allocation concealment | Blinding | Withdrawal and loss | Intention-to-treat analysis | Baseline characteristics | Jadad score | Quality Lesley (2004)[24] | Randomization list | Adequate | Not possible | Description | Used | Similar | 3 | A Lesley (2007)[25] | Randomization list | Adequate | Not possible | Description | Used | Similar | 3 | A Laura Berroeta (2007)[26] | Computer generated | Adequate | Not possible | Description | Used | Unclear | 3 | B Mosterd (2008)[27] | Computer generated | Unclear | Not possible | Description | Unclear | Similar | 3 | B Roozeboom (2013)[28] | Computer generated | Unclear | Not possible | Description | Unclear | Similar | 3 | B Complete Response Rate (M-H risk ratio): PDT und SE gleichwertig bzw. leichter Vorteil von PDT gegenüber SE • Nach 3 Monaten (2 Studien): 0.95 (95% CI 0.90, 1.00), I^2=0% • Nach 1 Jahr (3 Studien): 0.89 (95% CI 0.80, 0.99), I^2=0% • Nach 2 Jahren (3 Studien): 0.83 (95 % CI 0.69, 1.00), I^2=61% • Nach 3 Jahren (3 Studien): 0.73 (95% CI 0.63, 0.85), I^2=28% • Nach 4 Jahren (2 Studien): 0.84 (95% CI 0.65, 1.08), I^2=0% • Nach 5 Jahren (2 Studien): 0.79 (95% CI 0.61, 1.03), I^2=56% Cumulative probability of recurrence (M-H risk ratio): deutlich erhöhtes Risiko für ein Rezidiv bei Behandlung mit PDT gegenüber SE • Nach 1 Jahr (4 Studien): 5.28 (95% CI 1.85, 15.12), I^2=0% • Nach 2 Jahren (3 Studien): 6.48 (95 % CI 2.46, 17.09), I^2=0% • Nach 3 Jahren (2 Studien): 9.67 (95% CI 3.02, 30.99), I^2=0% • Nach 4 Jahren (2 Studien): 7.73 (95% CI 2.81, 21.28), I^2=33% • Nach 5 Jahren (2 Studien): 8.25 (95% CI 3.01, 22.62), I^2=41%
	4. Anmerkungen/Fazit der Autoren According to meta-analysis, PDT is comparably effective with SE but increases the risk of recurrence. 5. *Anmerkung FBMed: Studie hatte kein Fokus auf das fortgeschrittene Basalzellkarzinom, sondern umfasste Patienten in allen Krankheitsstadien. „Most tumors were within 10 mm (range 5–30 mm).“ -> vorwiegend leichte Krankheitsstadien*
Clark C et al., 2014 [1].	1. Fragestellung This review aims to provide a current analysis of evidence for the

Basal cell carcinoma: an evidence-based treatment update	treatment of BCC; specifically, which treatments have the lowest recurrence rates and the best cosmetic outcomes.
	2. Methodik Population: Patienten mit Basalzellkarzinom Intervention/Komparator: surgical therapy, radiotherapy and cryotherapy, photodynamic therapy (PDT), topical imiquimod, topical 5-fluorouracil (5-FU), topical solasodine glycoalkaloids, topical ingenol mebutate, intralesional 5-FU, intralesional interferon (IFN), and oral hedgehog pathway inhibitors. Endpunkt: BCC cure, and cosmetic outcome Suchzeitraum (Aktualität der Recherche): searched PubMed (January 1946 to August 2013), Ovid MEDLINE (2003–August 2013), the Cochrane Central Register of Controlled Trials (January 1993 to August 2013), and the Cochrane Database of Systematic Reviews (The Cochrane Library Issue 9, 2013) databases for randomized controlled trials, systematic reviews, or comparative studies for the treatment of BCC. Anzahl eingeschlossene Studien/Patienten (Gesamt): 40 studies: 29 randomized controlled trials (RCTs), seven systematic reviews, and four nonrandomized prospective trials. Qualitätsbewertung der Studien: Studies were judged on the quality of evidence (QOE) and strength of recommendation (SOR) for each treatment modality as described in the American College of Physicians' guideline grading system in 2010 [8]. 8. Qaseem A, Snow V, Owens DK, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153(3):194–9.
	3. Ergebnisdarstellung

Table 4 Summary of treatment modalities with strength of recommendation

Modality	SOR: low-risk tumor	SOR: high-risk tumor	QOE	Comments
MMS				
Standard [9, 49]	Strong	Strong	High	Preferred for facial, rBCC, H-zone, and aggressive HS. If cosmetically sensitive, MMS is tissue sparing. Primary tumors show equivalent CR with SE
Imiquimod pre-treatment [16]	Strong	Strong	Moderate	
Simple SE [9, 11–15, 48, 49]	Strong	Weak	Moderate	
PDT				
ALA-PDT [4, 19, 21–23, 48, 49]	Weak	Weak	Moderate	Some studies used outdated methods of PDT
MAL-PDT [4, 12, 20, 24, 46, 49]	Weak	Weak	Moderate	BCNS patients were included in the fractionated PDT trials
Fractionated ALA-PDT [4, 22, 23]	Strong	Weak	High	Preliminary data impressive for Er:YAG laser and PDT combination; long-term data are needed
Er:YAG laser + ALA-PDT [21]	Strong	Strong	Moderate	
Cryosurgery				
With curettage [11]	Weak	Weak	Low	Preliminary data for immunocryosurgery (cryosurgery during midcourse of imiquimod) are good; long-term data are needed
Concurrent imiquimod [17]	Insufficient data	Insufficient data	Moderate	
Subsequent imiquimod [17]	Weak	Weak	Moderate	Best reserved for non-surgical patients/sites, out of concern for long-term increased cancer risk
Radiotherapy [15, 18, 48]	Strong	Strong	Moderate	Lower cure rates make this inappropriate therapy for high-risk tumors Insufficient data on the use for small (<1 cm) nBCC
Topical imiquimod [2, 4, 16, 17, 24, 43–45]	Strong	NA	Moderate	
Topical 5-flourouracil [1, 24, 43]	Strong	NA	Moderate	Lower cure rates make this inappropriate therapy for high-risk tumors
Topical solasodine glycoalkaloids [34]	Insufficient data	NA	Moderate	Small studies had promising results, pending larger studies. Should be considered experimental treatment modality
Topical ingenol mebutate [35]	Weak	NA	Moderate	Small studies had promising results, pending larger studies. Should be considered experimental treatment modality
Intralesional IFN-α-2β [1, 2]	Weak	NA	Moderate	Small studies had promising results, pending larger studies. Cost of drug and associated AEs outweigh the benefits with this therapy due to better options for low-risk tumors
HPI: vismodegib [40]	NA	Strong	High	Indicated for use of aBCC, therefore not appropriate therapy for low-risk tumors due to drug risk outweighing therapeutic benefit

aBCC advanced BCC, *AE* adverse event, *ALA-PDT* aminolaevulinic acid photodynamic therapy, *BCC* basal cell carcinoma, *BCNS* basal cell nevus syndrome, *CR* clearance rate, *Er* erbium, *HPI* hedgehog pathway inhibitor, *HS* histological subtype, *H-zone* high-risk zone, *IFN* interferon, *MAL-PDT* methyl aminolaevulinate photodynamic therapy, *MMS* Mohs micrographic surgery, *NA* not applicable, *nBCC* nodular BCC, *PDT* photodynamic therapy, *QOE* quality of evidence, *rBCC* recurrent BCC, *SE* surgical excision, *SOR* strength of recommendation

4. Anmerkungen/Fazit der Autoren

Surgical methods remain the gold standard in BCC treatment, with Mohs micrographic surgery reserved for recurrent or high-risk lesions.

Suitable alternate treatment options for primary low-risk lesions include PDT, cryotherapy, topical imiquimod, and 5-FU.

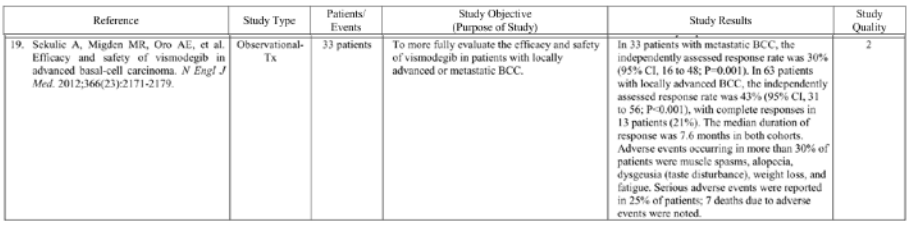
New hedgehog pathway inhibitors, such as vismodegib, appear to have some efficacy for the management of advanced BCC. However, side effects are a concern, and much remains to be learned regarding optimal treatment length, risk and timing of recurrence and potential development of resistance.

	5. Anmerkung FBMed: Interessenkonflikte des Letztautors vorhanden

Leitlinien

<table>
<tr><td>Koyfman SA et al., 2016 [6].

ACR Appropriateness Criteria Aggressive Nonmelanoma-tous Skin Cancer of the Head and Neck</td><td>Leitlinie des American College of Radiology
The ACR Appropriateness Criteria® (AC) are evidence-based guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decision for a specific clinical condition. Employing these guidelines helps providers enhance quality of care and contribute to the most efficacious use of radiology.</td></tr>
<tr><td></td><td>Methodik
Grundlage der Leitlinie:
Literatursuche in MEDLINE, Suchzeitraum: Januar 2003-December 2013, Qualitätsbewertung der Primärliteratur (Kriterien: Statistische Maßzahlen mit Fehler, Prospektives Design, systematisches Recruitment, Kontrollgruppe, Referenzmethoden, Random allocation, Länge des Follow-ups, Verwendung aller Teilnehmer (drop outs))
Definitions of Study Quality Categories
<table>
<tr><th>Study Quality Category Name</th><th>Study Quality Category Definition</th><th>Criteria for Diagnostic Studies</th><th>Criteria for Therapeutic Studies</th></tr>
<tr><td>Category 1</td><td>The study is well designed and accounts for common biases.</td><td>The source has all 8 diagnostic study quality elements present.</td><td>The source has 5 or 6 therapeutic study quality elements present.</td></tr>
<tr><td>Category 2</td><td>The study is moderately well designed and accounts for most common biases.</td><td>The source has 6 or 7 diagnostic study quality elements present.</td><td>The source has 3 or 4 therapeutic study quality elements present.</td></tr>
<tr><td>Category 3</td><td>The study has important study design limitations.</td><td>The source has 3, 4, or 5 diagnostic study quality elements present.</td><td>The source has 1 or 2 therapeutic study quality elements present.</td></tr>
<tr><td>Category 4</td><td>The study or source is not useful as primary evidence.
The article may not be a clinical study, the study design is invalid, or conclusions are based on expert consensus.
The study does not meet the criteria for or is not a hypothesis-based clinical study (eg, a book chapter or case report or case series description);
or
The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
or
The study is an expert opinion or consensus document.</td><td>The source has 0, 1, or 2 diagnostic study quality elements present.</td><td>The source has zero (0) therapeutic study quality elements.</td></tr>
<tr><td>Category M</td><td>Meta-analysis studies are not rated for study quality using the study element method because the method is designed to evaluate individual studies only. An “M” for the study quality will indicate that the study quality has not been evaluated for the meta-analysis study.</td><td>n/a</td><td>n/a</td></tr>
</table>
Kein Konsensusprozess beschrieben
Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt.</td></tr>
<tr><td></td><td>Keine Empfehlungen bezüglich Indikation, Evidenz wird folgendermaßen zusammengefasst/bewertet:</td></tr>
</table>

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med.* 2012;366(23):2171-2179.	Observational-Tx	33 patients	To more fully evaluate the efficacy and safety of vismodegib in patients with locally advanced or metastatic BCC.	In 33 patients with metastatic BCC, the independently assessed response rate was 30% (95% CI, 16 to 48; P=0.001). In 63 patients with locally advanced BCC, the independently assessed response rate was 43% (95% CI, 31 to 56; P<0.001), with complete responses in 13 patients (21%). The median duration of response was 7.6 months in both cohorts. Adverse events occurring in more than 30% of patients were muscle spasms, alopecia, dysgeusia (taste disturbance), weight loss, and fatigue. Serious adverse events were reported in 25% of patients; 7 deaths due to adverse events were noted.	2

Zloty D et al., 2015 [8].	<u>Canadian Non-Melanoma Skin Cancer Guidelines</u> Fragestellung/Zielsetzung: provide guidance to Canadian health care practitioners on Non-melanoma skin cancer management
Non-melanoma Skin Cancer in Canada Chapter 4: Management of Basal Cell Carcinoma	Methodik Grundlage der Leitlinie Guidelines Committee comprises 10 dermatologists and dermatologic surgeons Suche: PubMed search of English- language clinical trials was conducted bis August 2012 Studienbewertung (Table 2) und strength of each recommendation (Table 3) nach GRADE

Table 2. The GRADE System for Classifying the Quality of Evidence.[a]

Level of Evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Abbreviation: GRADE, Grading of Recommendations Assessment, Development and Evaluation.
[a]In addition, for statements based purely on biologic plausibility or other indirect arguments, the level of evidence could be identified as "NA," indicating that direct support for the claim is not available.

Table 3. Rating the Strength of Recommendations.

Strength of Recommendation	Definition
Strong	For intervention: desirable effects outweigh undesirable effects Against intervention: undesirable effects outweigh desirable effects
Weak	For intervention: desirable effects probably outweigh undesirable effects Against intervention: undesirable effects probably outweigh desirable effects, but appreciable uncertainty exists

	Studies rated as "moderate" quality or better by at least 1 Committee member served as the core literature authors were free to conduct additional, targeted searches and to provide further insights on the basis of personal experience and judgment Abstimmung über Leitlinie im Ganzen durch Panel (kein Konsensusprozess beschrieben) Endorsers and sponsors were not party to the development of the guidelines and were not involved in the literature search, the selection of Committee members, or the drafting of text, recommendations, or algorithms. Interessenkonflikte vorhanden und veröffentlicht Sonstige methodische Hinweise

	Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt.
	Empfehlungen bezüglich Indikation: | Recommendation	Level of Evidence[a]	Strength of Recommendation[b]
---	---	---
Patients with locally advanced or metastatic BCC should be referred for specialist care for discussion of possible vismodegib therapy	High[90,91,95]	Strong	 [a]Level of evidence (LoE) is evaluated as high, moderate, low, or very low, corresponding to the likelihood that the benefits of the therapeutic approach will stand up to further testing. Therapeutic approaches supported by meta-analyses or multiple randomized control trials (RCTs) that are free from significant bias have a high LoE. Studies based on intra-individual comparisons may also have a high LoE. Options supported by methodologically weaker (non-RCT) studies and those with weak effects or inconsistent data across studies have a low or very low LoE. Statements that are based on biological plausibility or other indirect arguments are listed as NA, indicating that direct support for the claim is not available. (See Chapter 1 for general methods.) [b]Strength of recommendation is evaluated as strong or weak, depending on the confidence that the treatment is more helpful than the alternative(s), including nontreatment. Hence, therapies with a high LoE regarding efficacy may receive a weak recommendation if the risk of adverse response is high or if this risk is not well known. Conversely, approaches with no likelihood of doing harm may receive a strong recommendation, even if they are supported by limited evidence. (See Chapter 1 for general methods.) Early trials of vismodegib have shown response rates ranging from 30% to 50% and 43% to 60% in metastatic and locally advanced BCC, respectively.[90,91] The major limitations of vismodegib therapy are high cost ($7500 USD per month, for an average of 10 months) and toxicity (grade 1-2 hair loss, muscle cramps,and taste disturbance).[92] Literatur: 90. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med. 2009;361(12):1164-1172. 91. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012;366(23):2171-2179. 92. Poggi L, Kolesar JM. Vismodegib for the treatment of basal cell skin cancer. Am J Health Syst Pharm. 2013;70(12):1033-1038. 95. Grob JJ, Kunstfeld R, Dreno B, et al. Vismodegib, a Hedgehog pathway inhibitor (HPI), in advanced basal cell carcinoma (aBCC): STEVIE study interim analysis in 300 patients. J Clin Oncol. 2013;31(supplement):Abstract 9036.
Trakatelli M et al., 2014 [7]. Update of the European guidelines for basal cell carcinoma management	Developed by Guideline Subcommittee of the European Dermatology Forum Fragestellung/Zielsetzung: To present updated guidelines that include consensual expert definitions on various BCC types, prognosis and risk factors for BCC as well as review recommendations for diagnosis and treatment reflecting current published evidence.
	Methodik Grundlage der Leitlinie based on the initial EDF guidelines published in 2006, the French guidelines and the British Association of Dermatologists' guidelines published in 2006 and 2008 These guidelines (S1 type), were prepared by the BCC subgroup of the European Dermatology Forum (EDF)'s guidelines committee Literature analysis was based on Pubmed searches (up to 2012) and papers were graded on the basis of supporting evidence Quality of evidence I Evidence obtained from at least one properly designed, randomized controlled trial.

	II-i Evidence obtained from well-designed controlled trials without randomization. II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group. II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence. III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees. IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence). Strength of recommendations A There is good evidence to support the use of the procedure. B There is fair evidence to support the use of the procedure. C There is poor evidence to support the use of the procedure. D There is fair evidence to support the rejection of the use of the procedure. E There is good evidence to support the rejection of the use of the procedure. Keine Angabe zum Konsensusprozess Sonstige methodische Hinweise *Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt.*
	Empfehlungen (mit Bezug zur Indikation) C. LOCALLY ADVANCED OR METASTATIC BCC: **1. Chemotherapy** **- Presently no level of evidence supports the use of chemo-therapy in the treatment of advanced BCC (Strength of recommendation: C, Quality of evidence IV)** No standard therapy for metastatic BCC or even for cases of locally advanced tumours exists. Due to the absence of randomized trials or even large case series, treatment is guided by anecdotal evidence or the availability of clinical trials. Published data suggest that platinum-based therapy can induce responses in metastatic BCC and should be considered first for such patients if treatment is warranted [155-157]. 155. Guthrie TH Jr., Porubsky ES, Luxenberg M, et al. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. J Clin Oncol 1990; 8: 342-6. 156. Moeholt K, Aagaard H, Pfeiffer P, Hansen O. Platinum-based cytotoxic therapy in basal cell

carcinoma – a review of the literature. Acta Oncol 1996; 35: 677-82.
157. Carneiro BA, Watkin WG, Mehta UK, et al. Metastatic basal cell carcinoma: complete response to chemotherapy and associated pure red cell aplasia. Cancer Invest 2006; 24: 396-400.

2. Targeted Therapy

- Anti-smo agents are effective against locally-advanced or metastatic BCC (Strength of recommendation A, Quality of evidence II-i)

In phase I clinical trials, patients affected by locally advanced BCC (laBCC) and metastatic BCCs (mBCC) were treated with 150-270 mg/day of a synthetic SMO inhibitor (GDC-0449 or vismodegib) for a median of 10 months. The overall response rate was 60% in laBCC and 50% in mBCC [159, 160]. In a subsequent phase II trial that included 104 patients treated with vismodegib 150 mg once daily for a median of 7.6 months, the response rate was 42.9% in laBCC and 30.3% in mBCC [161]. In both phase I and II trials, the mean duration of clinical response was eight months. Notably, a significant decrease of the size of existing BCCs and reduction of newly developed BCCs were described in a double blind phase II trial on 41 patients with NBCCS treated with vismodegib for at least eight months [162]. The most common side effects were muscle spasms, dysgeusia, hair loss and fatigue.

Long-term use of vismodegib is limited by these side effects; indeed, almost half of NBCCS patients discontinue the drug because of them. Clinical studies are being developed to check if intermittent doses (on and off treatment protocols) can improve tolerance without reducing efficacy.

159. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med 2009; 361: 1164-72.
160. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. Clin Cancer Res 2011; 17: 2502-11.
161. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med 2012; 366: 2171-9.
162. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 2012; 366: 2180-8.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 08.08.2017

#	Suchfrage
1	MeSH descriptor: [Neoplasms, Basal Cell] explode all trees
2	MeSH descriptor: [Carcinoma, Basal Cell] explode all trees
3	basal:ti next cell:ti
4	non-melanoma*:ti or nonmelanoma*:ti
5	skin:ti
6	basalioma*:ti or epithelioma*:ti
7	cancer:ti,ab,kw or mass:ti,ab,kw or tumour*:ti,ab,kw or tumor*:ti,ab,kw or carcinom*:ti,ab,kw or neoplas*:ti,ab,kw or adenocarcinoma*:ti,ab,kw or pigmented:ti,ab,kw
8	(#3 or #4 or #5) and #7
9	#1 or #2 or #6 or #8
10	#9 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 08.08.2017

#	Suchfrage
1	("neoplasms, basal cell"[MeSH]) OR "carcinoma, basal cell"[MeSH]
2	basal[Title/Abstract] AND cell[Title/Abstract]
3	((non-melanoma*[Title/Abstract]) OR nonmelanoma*[Title/Abstract]) AND skin[Title/Abstract]
4	(((((((((cancer[Title/Abstract]) OR mass[Title/Abstract]) OR tumour*[Title/Abstract]) OR tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR carcinom*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR lesion*[Title/Abstract]) OR pigmented[Title/Abstract]
5	(#2 OR #3) AND #4
6	basalioma*[Title/Abstract] OR (epithelioma*[Title/Abstract] AND skin[Title/Abstract])
7	#1 OR #5 OR #6
8	(#7) 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]))))
9	(#8) AND ((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract])
10	((#9) AND ("2012/08/01"[PDAT] : "2017/08/08"[PDAT]) NOT "The Cochrane database of

	systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 08.08.2017

#	**Suchfrage**
1	("neoplasms, basal cell"[MeSH]) OR "carcinoma, basal cell"[MeSH]
2	basal[Title/Abstract] AND cell[Title/Abstract]
3	((non-melanoma*[Title/Abstract]) OR nonmelanoma*[Title/Abstract]) AND skin[Title/Abstract]
4	(((((((((cancer[Title/Abstract]) OR mass[Title/Abstract]) OR tumour*[Title/Abstract]) OR tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR carcinom*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR lesion*[Title/Abstract]) OR pigmented[Title/Abstract]
5	(#2 OR #3) AND #4
6	basalioma*[Title/Abstract] OR (epithelioma*[Title/Abstract] AND skin[Title/Abstract])
7	#1 OR #5 OR #6
8	(#7) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
9	(#9) AND ("2012/08/01"[PDAT] : "2017/08/31"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal]))

Literatur:

1. **Clark CM, Furniss M, Mackay-Wiggan JM.** Basal cell carcinoma: an evidence-based treatment update. Am J Clin Dermatol 2014;15(3):197-216.

2. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vismodegib vom 4. August 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 08.08.2017]. URL: https://www.g-ba.de/downloads/39-261-2672/2016-08-04_AM-RL-XII_Vismodegib_D-213_BAnz.pdf.

3. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Vismodegib - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-09 [online]. Köln (GER): IQWiG; 2016. [Zugriff: 07.08.2017]. (IQWiG-Berichte; Band 392). URL: https://www.iqwig.de/download/A16-09_Vismodegib_Nutzenbewertung-35a-SGB-V.pdf.

4. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Vismodegib (Basalzellkarzinom) - Addendum zum Auftrag A16-09; Addendum; Auftrag A16-40 [online]. Köln (GER): IQWIG; 2016. [Zugriff: 07.08.2017]. (IQWiG-Berichte; Band 410). URL: https://www.iqwig.de/download/A16-40_Vismodegib_Addendum-zum-Auftrag-A16-09.pdf.

5. **Jacobsen AA, Aldahan AS, Hughes OB, Shah VV, Strasswimmer J.** Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma: A Systematic Review and Pooled Analysis of Interventional Studies. JAMA Dermatol 2016;152(7):816-824.

6. **Koyfman SA, Cooper JS, Beitler JJ, Busse PM, Jones CU, McDonald MW, et al.** ACR Appropriateness Criteria((R)) Aggressive Nonmelanomatous Skin Cancer of the Head and Neck. Head Neck 2016;38(2):175-182.

7. **Trakatelli M, Morton C, Nagore E, Ulrich C, Del Marmol V, Peris K, et al.** Update of the European guidelines for basal cell carcinoma management. Eur J Dermatol 2014;24(3):312-329.

8. **Zloty D, Guenther LC, Sapijaszko M, Barber K, Claveau J, Adamek T, et al.** Non-melanoma Skin Cancer in Canada Chapter 4: Management of Basal Cell Carcinoma. J Cutan Med Surg 2015;19(3):239-248.

9. **Zou Y, Zhao Y, Yu J, Luo X, Han J, Ye Z, et al.** Photodynamic therapy versus surgical excision to basal cell carcinoma: meta-analysis. J Cosmet Dermatol 2016;15(4):374-382.