Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-146 Cemiplimab

Stand: Juli 2020

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

Cemiplimab

[lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), zuvor mit einem Hedgehog-Inhibitor behandelt **]**

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	Vismodegib – Beschluss vom 04.08.2016 Sonidegib - Beschluss vom 02.08.2018
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: Cemiplimab	
Cemiplimab L01XC33 LIBTAYO®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Cemiplimab ist indiziert zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden.
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 b**ei 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).
Sonidegib L01XX48 Odomzo®	Odomzo ist angezeigt für die Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem Basalzellkarzinom (BZK), die für eine kurative Operation oder eine Strahlentherapie nicht in Frage kommen.

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-146 (Cemiplimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	8. Juli 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCC	Basalzellkarzinom
ECRI	ECRI Guidelines Trust
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
laBCC	Lokal fortgeschriffenes Basalzellkarzinom
LoE	Level of Evidence
mBCC	Metastasiertes Basalzellkarzinom
MMS	Mohs micrographic surgery
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PDT	Photodynamische Therapie
RR	Relatives Risiko
SCC	Plattenepithelkarzinom
SIGN	Scottish Intercollegiate Guidelines Network
SMO	smoothened (inhibitor)
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Basalzellkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 11.06.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, CCO, ECRI, ESMO, G-BA, GIN, NCCN, NCI, 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 590 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 4 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [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 2. August 2018 - Sonidegib

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

Vismodegib

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [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 4. August 2016 - Vismodegib

Anwendungsgebiet

erwachsenen Patienten mit:

• symptomatischem metastasiertem Basalzellkarzinom

• lokal fortgeschrittenem Basalzellkarzinom, bei denen eine Operation oder Strahlentherapie nicht geeignet ist (siehe Abschnitt 5.1 der Fachinformation).

Zweckmäßige Vergleichstherapie

a) Erwachsene Patienten mit symptomatischem metastasiertem Basalzellkarzinom

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.

b) Erwachsene Patienten mit lokal fortgeschrittenem Basalzellkarzinom, für die weder eine Operation noch eine Strahlentherapie geeignet ist

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 des Zusatznutzens

a) Erwachsene Patienten mit symptomatischem metastasiertem Basalzellkarzinom

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit lokal fortgeschrittenem Basalzellkarzinom, für die weder eine Operation noch eine Strahlentherapie geeignet ist

Anhaltspunkt für einen geringen Zusatznutzen.

3.2 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten Quellen identifiziert.

3.4 Leitlinien

Peris K et al., 2019 [4].

European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC)

Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines

Zielsetzung/Fragestellung

The present guidelines contain recommendations with regard to the diagnosis, therapy and follow-up of patients with BCC, addressing in detail all aspects of BCC management, from the common types of tumours to those which are ‘advanced’ or ‘difficult to treat’.

Methodik

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

Grundlage der Leitlinie

- Multidisziplinäres Gremium, Patientenbeteiligung wird nicht beschrieben;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Leitlinie basiert auf updated EDF guidelines, the German S2k guidelines, the French guidelines and the British Association of Dermatologists’ guidelines + zusätzlich Suche in Medline, keine Angaben zur Auswahl und Bewertung der Evidenz (Es wird auf AGREE II Methodik verwiesen).
- Formale Konsensusprozesse dargelegt;
- Ein externes Begutachtungsverfahren wird nicht beschrieben.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- De novo literature search was conducted by the authors by Medline search.
- Keine Angabe zum Recherchedatum

LoE

Oxford levels of evidence Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.

Question	Step 1 (Level 1[a])	Step 2 (Level 2[a])	Step 3 (Level 3[a])	Step 4 (Level 4[a])	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances[b]	Local non-random sample[b]	Case series[b]	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional studies with consistently applied reference standard and blinding	Non-consecutive studies or studies without consistently applied reference standards[b]	Case-control studies, or poor or non-independent reference standard[b]	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomised trial[a]	Case series or case-control studies, or poor-quality prognostic cohort study[b]	n/a
Does this intervention help? (Treatment benefits)	Systematic review of randomised trials or *n*-of-1 trials	Randomised trial or observational study with dramatic effect	Non-randomised controlled cohort/follow-up study[b]	Case series, case-control studies or historically controlled studies[b]	Mechanism-based reasoning
What are the *common* harms? (Treatment harms)	Systematic review of randomised trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about or observational study with dramatic effect	Individual randomised trial or (exceptionally) observational study with dramatic effect	Non-randomised controlled cohort/follow-up study (postmarketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms, the duration of follow-up must be sufficient.)[b]	Case series, case-control or historically controlled studies[b]	Mechanism-based reasoning
What are the *rare* harms? (Treatment harms)	Systematic review of randomised trials or *n*-of-1 trial	Randomised trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomised trials	Randomised trial	Non-randomised controlled cohort/follow-up study[b]	Case series, case-control or historically controlled studies[b]	Mechanism-based reasoning

[a] Level may be graded down on the basis of study quality, imprecision and indirectness (study PICO does not match questions PICO) because of inconsistency between studies or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. PICO, P (Patient, Population, or Problem), I (Intervention), C (Comparison), O (Outcome).
[b] As always, a systematic review is generally better than an individual study.

GoR

Grades of recommendation.

Grade of recommendation	Description	Syntax
A	Strong recommendation	shall
B	Recommendation	should
0	Recommendation pending	may/can

Classification

We consider a more pragmatic and operational classification for BCC is into ‘easy-to-treat’ BCC, which includes the most ‘common BCC’, and ‘difficult-to-treat’ BCC (submitted). More than 95% of BCCs are easy to treat through standard surgery or a range of alternative blind treatments at least during the initial months or years after diagnosis. Difficult-to-treat BCCs include ‘all locally advanced BCCs’ and also common BCCs which, for any reason, pose specific management problems. These reasons may be (1) the technical difficulty of maintaining function and aesthetics due to the size or location (eyes, nose, lips and ears) of the tumour; (2) the poorly defined borders often associated with morphoeic subtype or prior recurrence; (3) multiple prior recurrences on the face (often requiring much larger excision); (4) prior radiotherapy; (5) patient’s reluctance to accept the consequences of surgery and (6) patient’s comorbidities interfering with surgery.

3. Management of common (easy-to-treat) BCC

3.1. Primary therapy

Most primary BCCs can be easily treated by surgery or by non-surgical methods for certain subtypes. BCCs with high risk of recurrence need to be treated more aggressively. Risk of recurrences increases with tumour size, poorly defined margins, aggressive histological subtype or previous recurrences. Certain tumours can be locally advanced with destruction of adjacent tissues or difficult to treat for other reasons which might need discussion regarding appropriate therapy in a multidisciplinary board.

Surgery	Evidence-based recommendation
Grade of recommendation A	Surgical removal is highly effective to treat BCC and allows histological confirmation
Level of evidence 3	Guideline adaption [1] Strength of consensus: 100%

3.1.1. Which BCC should be excised?

Surgical excision is a very effective treatment for primary BCC treatment, with recurrence rates varying from less than 2% - 8% at 5 years after surgery (reviewed in the study by Trakatelli et al. [1]). Scalpel excision is performed using either a standard (2D) excision with safety margins or a microscopically controlled stepwise procedure (3D excision).

Alternatively, surgical removal by destructive (blind) treatments and non-surgical modalities including topical treatments or photodynamic therapy (PDT), either alone or combined, may be used for low-risk BCCs when surgery is contraindicated or impractical.

4. Management of 'difficult-to-treat' BCC

4.1. Surgical therapy

4.1.1. When should we still consider surgery for ‚difficult-to-treat' BCC?

Surgery can be considered as a primary therapeutic option, as a palliative option and also following a neoadjuvant approach attempting to reduce the extent of the surgical procedure. The appropriate management should be carefully planned in a skin cancer multidisciplinary board wherein the potential strategies on surgical excision, reconstruction, tissue preservation, indications for prosthesis and radiotherapy are discussed. Appropriate imaging to determine the extent of the tumour is indicated when perineural involvement or bone invasion is suspected [48,103].

Surgery of difficult-to-treat BCC	Consensus-based recommendation
GCP	Decision on the potential suitability, indication and technique in difficult-to-treat BCC shall be made in a multidisciplinary team Strength of consensus: 100%

4.2. Medical therapy

4.2.1. Hedgehog inhibition

4 . 2 . 1 . 1 . What are the i n d i c a t i o n s f o r Hedgehog inhibition?.

Vismodegib and sonidegib are specific inhibitors of an oncogenic protein named Smoothened approved by the FDA and EMA, and both are both indicated for the treatment of patients with laBCC who are not good candidates for surgery or radiotherapy, while vismodegib is also approved for mBCC [30,104]. The approved oral dose is 150 mg/day for vismodegib and 200 mg/day for sonidegib. Vismodegib was the first approved Hh inhibitor. A phase 2 pivotal clinical trial (ERIVANCE) in 104 patients with laBCC and mBCC showed initially a response rate of 48% (laBCC) and 33% (mBCC) and a median response duration of 9.5 and 7.6 months, respectively [105]. An update on ERIVANCE after 39 months of follow-up showed a response rate of 60.3% for laBCC and 48.5% for mBCC. Twenty of 60 patients with laBCC showed a complete response. Of note, in patients with mBCC, there were no complete but only partial responses. The median response duration in the updated study results was 14.8 months (mBCC) and 26.2 months (laBCC). The median survival for patients with mBCC was 33.4 months and has not been reached for the patients with laBCC [105]. The results of the pivotal trial (ERIVANCE) have been confirmed by a global safety study SafeTy Events in VIsmodEgib (STEVIE) [106]. A STEVIE update revealed a response rate of 68.5% for laBCCs and 36.9% for mBCCs after a median follow-up of 17.9 months.

Another approved drug, which has been subsequently introduced to the market in many countries, is sonidegib. The pivotal clinical trial Basal Cell Carcinoma Outcomes with

LDE225Treatment (BOLT) was a prospective randomised double blinded trial of a 200 mg dose compared with an 800 mg dose once daily; the FDA and EMA approved the 200 mg dose based on the risk/benefit ratio. The response rate assessed in the initial study, which had very stringent modified RECIST criteria, was 36% [25]. In a 12-month analysis of the BOLT trial, the response rate for the 200 mg group improved to 57.6% for laBCC and 7.7% for mBCC [107]. The last BOLT update published after a median follow-up of 30 months [108] reported a response rate of 56.1% (central review) and 71.2% (response evaluation by investigator). The corresponding response rates for mBCCs were 7.7% and 23.1%. The median duration of responses was 26.1 months (laBCC) and 24.0 months (mBCC). The median survival has not been reached in the two groups. However, the 2-year survival rate was 93.2% (laBCC) and 69.3% (mBCC).

Multiple BCCs in patients with NBCCS should be considered as laBCCs and treated accordingly. They have been included as small subgroups in the pivotal clinical trials on vismodegib (ERIVANCE) and sonidegib (BOLT).

In laBCCs, a neoadjuvant treatment with an Hh inhibitor with the intention to shrink lesions can be discussed, but there are no randomised data to prove ist beneficial outcome. In a series of 15 patients treated with vismodegib for 3-6 months before surgery, only 1 patient recurred after 22 months [109,110].

Radiotherapy could be used in complicated cases in combination with vismodegib [111] and may be indicated after surgery when perineural invasion is present [112].

Hedgehog inhibitors	Evidence-based recommendation
Grade of recommendation B	Hh inhibitors should be offered to patients with locally advanced or metastatic BCCs
Level of evidence 3	De novo literature search [104] Strength of consensus: 100%

4.2.2. Chemotherapy

4.2.2.1. Is there a place for chemotherapy in difficult-to-treat BCC?

The use of systemic chemotherapy for mBCC has been addressed only in case reports and case series [117]. Most patients with widespread metastases receive platinum-based chemotherapies. These patients are typically treated similar to patients with metastatic SCC. The response rate is not higher than 20-30%, but occasionally response rates up to 60% are reported. However, in almost all of the successfully treated cases, the response duration was no longer than 2-3 months [30].

Chemotherapy might be considered for laBCC and mBCC as second- or third-line treatment in patients who are not responsive or have progressed after Hh inhibitors, often in combination with radiotherapy. However, if currently ongoing studies on therapy with PD1-immune checkpoint inhibitors show significant activity in BCC, chemotherapy might remain as a lastline treatment.

Chemotherapy	Consensus-based recommendation
GCP	The use of chemotherapy in the treatment of BCC can be discussed if Hh inhibitors are contraindicated and no clinical trials are available Strength of consensus: 100%

4.2.3. Immunotherapy

4.2.3.1. Is there already a place for immunotherapy in difficult-to-treat BCC?.

It is well known that BCCs are carrying a high mutational load induced by the total carcinogen UV light. According to the current knowledge on the relationship of mutational load and response to immune checkpoint inhibitors, BCCs could be considered as ideal candidates for a response to immunotherapies. There are anecdotal reports about responses to anti-PD-1 agents such as nivolumab or pembrolizumab in treatment-naı¨ve and treatment-refractory patients with laBCC and mBCCs [118,119]. Of interest, also patients who received Hh inhibitors and failed to respond have subsequently been treated successfully with immune checkpoint inhibitors. However, data from clinical trials are so far lacking.

The efficacy of nivolumab, alone or in combination with ipilimumab, and of cemiplimab (REGN2810), a PD-1 antibody recently approved for locally advanced and metastatic cSCC, is currently being investigated in patients with laBCC and mBCC in two independent phase 2 clinical trials (https://clinicaltrials.gov). In addition, in a proof-of-principle study, pembrolizumab was shown to be active against advanced BCCs and the response rate of the pembrolizumab plus vismodegib group was not superior to the monotherapy group [120].

5. Radiotherapy of BCC

During recent decades, radiotherapy has been reported as a valid alternative to surgery. The risk of developing a radiotherapy-induced secondary skin cancer is negligible using required radiation doses to treat cutaneous carcinomas. In contrast, a high risk exists in patients treated with lower doses for benign cutaneous conditions [121,122].

…

The main indications for radiotherapy are either inoperable tumours or when the tumour board considers the certainty of disfigurement is not balanced by a certainty of clear margins. Although it has not been evaluated as an adjuvant therapy, radiotherapy may be also considered after incomplete resection with microscopic (R1) or macroscopic (R2) residual tumour, when the tumour board does not consider follow-up or a new resection as the best option.

Radiotherapy	Consensus-based recommendation
Grade of recommendation A	In BCC on the face including periorbital regions and other anatomical regions, radiotherapy is an alternative to surgery in elderly patients and in patients who are not candidates for surgery
Level of evidence 1	De novo literature search [123] Strength of consensus: 100%

Referenzen aus Leitlinien

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American Academy of Dermatology

Guidelines of care for the managementof basal cell carcinoma

Zielsetzung/Fragestellung

The main focus of the guideline is on the most commonly considered and utilized approaches for the surgical and medical treatment of primary BCC, but it also includes recommendations on the treatment of recurrent tumors when applicable, appropriate biopsy techniques, staging, follow-up, and prevention of BCC.

Methodik

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

<u>Grundlage der Leitlinie</u>

- Repräsentativität des Gremiums unklar, Patientenbeteiligung nicht beschrieben;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche und Auswahl der Evidenz, eine Bewertung des Risk of Bias der eingeschlossenen Studien wird nicht beschrieben;
- Konsensusprozesse nicht beschrieben, externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Systematic search and review of published studies from PubMed and the Cochrane Library databases from January 1960 through April 2015 for all identified clinical questions. A secondary search was subsequently undertaken to identify and review published studies from April 2015 to August 2016 to provide the most current information.

LoE

Evidence was graded using a 3-point scale based on the quality of study methodology (eg, randomized controlled trial [RCT], case-control, prospective/retrospective cohort, case series, etc) and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

- I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
- II. Limited-quality patient-oriented evidence.
- III. Other evidence, including consensus guidelines, opinion, case studies, and diseaseoriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

GoR

A. Recommendation based on consistent and good-quality patient-oriented evidence.

B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.

C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

Empfehlungen

Surgical Therapy

Table VII. Recommendations for the surgical treatment of BCC

A treatment plan that considers recurrence rate, preservation of function, patient expectations, and potential adverse effects is recommended.
C&E may be considered for low-risk tumors in non–terminal hair–bearing locations.
For low-risk primary BCC, surgical excision with 4-mm clinical margins and histologic margin assessment is recommended.
Standard excision may be considered for select high-risk tumors. However, strong caution is advised when selecting a treatment modality without complete margin assessment for high-risk tumors.
Mohs micrographic surgery is recommended for high-risk BCC.

BCC, Basal cell carcinoma; *C&E*, curettage and electrodessication.

Table VIII. Level of evidence and strength of recommendations for the surgical treatment of BCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment plan	A	II	31,41
C&E for low-risk tumors	B	I, II	24,31,36,42-45 35-41,46-58
Standard excision with 4-mm margins			
• Low-risk BCC	A	I	Expert opinion
• High-risk BCC	C	III	
MMS for high-risk BCC	A	I, II	17,32,33,42,43,49,50

BCC, Basal cell carcinoma; *C&E*, curettage and electrodessication; *MMS*, Mohs micrographic surgery.

Nonsurgical therapy

Table IX. Recommendations for the nonsurgical therapy of BCC

Cryosurgery may be considered for low-risk BCC when more effective therapies are contraindicated or impractical.
If surgical therapy is not feasible or preferred, topical therapy (eg, imiquimod or 5-FU), MAL- or ALA-PDT, and radiation therapy (eg, superficial radiation therapy, brachytherapy, external electron beam, and other traditional radiotherapy forms for BCC) can be considered when tumors are low risk, with the understanding that the cure rate may be lower.
Adjustment of topical therapy dosing regimen on the basis of side effect tolerance is recommended.
There is insufficient evidence to recommend the routine use of laser or electronic surface brachytherapy in the treatment of BCC.

ALA, Aminolevulinic acid; *BCC*, basal cell carcinoma; *5-FU*, 5-fluorouracil; *MAL*, methylaminolevulinate; *PDT*, photodynamic therapy.

Table X. Level of evidence and strength of recommendations for the nonsurgical treatment of BCC as alternatives to surgical therapy

Recommendation	Strength of recommendation	Level of evidence	References
Cryosurgery	A	I	36,41,46,60-63
Topical therapy			
• Imiquimod	A	I	39,64-77
• 5-FU	B	I, II	46,64,74-76,78,79
• Dose adjustments	A	I	39,68,70
PDT			
• ALA	A	I, II	38,47,61,74,76,77,80-85
• MAL	A	I, II	35,37,60,64,74,76,77,83,86,87
Radiation therapy			
• Traditional radiotherapies and modern superficial radiation therapy	B	I, II	23,34,42,43,46,62,88,89
• Electronic surface brachytherapy	C	II, III	90-92
Laser therapy	C	II	74,93,94

ALA, Aminolevulinic acid; *BCC*, basal cell carcinoma; *5-FU*, 5-fluorouracil; *MAL*, methylaminolevulinate.

MANAGING PATIENTS WITH METASTATIC AND ADVANCED BASAL CELL CARCINOMA

Table XI. Recommendations for managing locally advanced or metastatic BCC

Multidisciplinary consultation and smoothened inhibitors are recommended for patients with metastatic BCC.
If treatment of metastatic BCC with smoothened inhibitors is not feasible, platinum-based chemotherapy or best supportive care is recommended.
If surgery and radiation therapy are contraindicated or inappropriate for the treatment of locally advanced BCC, or if residual tumor persists following surgery and/or radiation therapy and further surgery and radiation therapy are contraindicated or inappropriate, systemic therapy with a smoothened inhibitor should be considered.
Patients with advanced disease should be provided with or referred for best supportive and palliative care, to optimize symptom management and maximize quality of life.

BCC, Basal cell carcinoma.

Table XII. Level of evidence and strength of recommendations for the management of metastatic BCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment with SMO inhibitors			
• Metastatic and Locally advanced BCC	A	I, II	107-111,113,114
• Gorlin syndrome	B	I	115
Platinum-based chemotherapy for metastatic BCC	C	III	106
Palliative care	C	III	Expert opinion

BCC, Basal cell carcinoma; *SMO*, smoothened.

Until recently, no approved therapy was available for metastatic BCC, and studies were limited to case reports and series using primarily platinum-based chemotherapeutic agents.[106] In 2012, Sekulic et al, reported an objective response rate of 30% among 33 patients with metastatic BCC treated with vismodegib, a smoothened (SMO) inhibitor targeted at the hedgehog pathway, according to the Response Evaluation Criteria in Solid Tumors.[107] After 12 months of additional follow-up, the objective response rate increased to 33%.[108] Although all the responses were partial, the majority of patients (73%) experienced tumor shrinkage, with a median duration of objective response of 7.6 months. Similar findings were reported in the Safety Events in

Vismodegib (STEVIE) trial, in which an overall response rate of 37.9% was found among 29 patients with metastatic BCC.[109] Oral vismodegib has been approved by the US Food and Drug Administration as the first systemic therapy for metastatic BCC.

Few other treatment options are available for patients with metastatic BCC. When metastatic disease is limited to the regional lymph node basin, surgery and/or radiation therapy remain the most appropriate treatment, when possible. For patients with distant metastases, multidisciplinary consultation is recommended to consider systemic therapy with hedgehog pathway inhibitors. If this is not feasible, platinum-based chemotherapy may be considered. Patients with advanced disease should also be provided with or referred to best supportive and palliative care to optimize symptom management and maximize quality of life.

Locally destructive tumors, which are typically associated with long delays in presentation, are encountered more often than metastatic BCC and may pose a significant therapeutic dilemma. Although surgery and radiation therapy remain the criterion standard of therapy, curative treatment may be associated with substantial morbidity. In the study by Sekulic et al, the efficacy of vismodegib was also evaluated in patients with locally advanced BCC.[107] Patients had at least 1 tumor 10 mm or larger in diameter that was considered inoperable or inappropriate for surgery in the opinion of a specialist in MMS, head and neck surgery, or plastic surgery. Inoperable or inappropriate for surgery was defined as either (1) the recurrence of BCC after 2 or more surgical procedures and an expectation that curative resection would be unlikely, or (2) substantial morbidity or deformity anticipated from surgery. In the cohort of 63 patients with locally advanced BCC, the objective response rate was 43%, with complete responses in 13 patients (21%) and a median duration of response of 7.6 months. After 12 months of additional follow-up, the objective response rate increased to nearly 48%, with a median duration of response of 9.5 months.[108] However, drug toxicity was substantial, with serious adverse events reported in 26 patients (25%). Higher response rates among 453 patients with locally advanced BCC were reported in the STEVIE trial, with an overall response rate of 66.7%.109 Notably, 180 of 499 patients in the STEVIE trial (36%) discontinued treatment because of adverse events, 108 (22%) were recorded as having serious adverse events, and among 31 deaths during the trial, 21 were the result of adverse events.

Routine adverse events that patients find troublesome include muscle spasms and arthralgias, alopecia, and dysgeusia often culminating in weight loss. Thirteen patients (12%) discontinued the study because of adverse events and 7 patients (1 with metastatic and 6 with locally advanced disease) died, though the relationship between vismodegib and the deaths was unknown.

Comparable findings were more recently reported with use of another SMO inhibitor, sonidegib, in patients with locally advanced BCC.110 At the 12-month analysis of the BCC Outcomes with LDE225 Treatment (BOLT) trial, response rates of 44% to 58% overall were found in patients with locally advanced BCC and 8% to 17% in patients with metastatic BCC.[111] There is initial evidence that patients resistant to one SMO inhibitor may be resistant to another.[112] Although the same limitations regarding adverse events and drug resistance apply, SMO inhibitors may be considered for patients with nevoid BCC (Gorlin) syndrome with excessively numerous or aggressive BCCs.

For localized BCC, the overwhelming majority of tumors are readily treated with local treatment modalities, including surgery, radiation therapy, and topical therapy. If surgery and radiation therapy are contraindicated or inappropriate for the treatment of locally advanced tumors, or if residual tumor persists following surgery and/or radiation therapy and further surgery and radiation therapy are contraindicated or inappropriate, multidisciplinary consultation is advised

to consider systemic therapy with a hedgehog pathway inhibitor. It is acknowledged by the work group that locally advanced, inoperable, inappropriate, and substantial morbidity or deformity from surgery are subjective and highly operator-dependent terms. Therefore, multidisciplinary consultation is strongly encouraged.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2020) am 11.06.2020

#	Suchfrage
#1	[mh "Basal Cell Carcinoma"] OR [mh "Basal Cell Neoplasms"]
#2	[mh "Skin Cancer"]
#3	(rodent NEAR/3 ulcer*):ti,ab,kw OR (basaliom*):ti,ab,kw
#4	(basal NEAR/3 cell*):ti,ab,kw OR (basocellular*):ti,ab,kw OR (skin):ti
#5	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan* OR Epithelioma*):ti,ab,kw
#6	#4 AND #5
#7	#1 OR #2 OR #3 OR #6
#8	#7 with Cochrane Library publication date Between Jun 2015 and Jun 2020

Systematic Reviews in Medline (PubMed) am 11.06.2020

#	Suchfrage
1	Carcinoma, Basal Cell[mh] OR Neoplasms, Basal Cell[mh]
2	(Rodent[Title/Abstract] AND ulcer*[Title/Abstract]) OR (basaliom*[Title/Abstract])
3	(Basal[Title/Abstract] AND cell*[Title/Abstract]) OR (basocellular*[Title/Abstract])
4	(skin[Title/Abstract]) AND (nonmelanoma*[Title/Abstract] OR non-melanoma*[Title/Abstract])
5	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab] OR Epithelioma*[tiab]
6	(#3 OR #4) AND #5
7	#1 OR #2 OR #6
8	(#7) 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]))))))
9	(#8) AND ("2015/06/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 11.06.2020

#	**Suchfrage**
1	Carcinoma, Basal Cell[mh] OR Neoplasms, Basal Cell[mh] OR Skin Neoplasms[Mesh Major Topic]
2	(Rodent[Title/Abstract] AND ulcer*[Title/Abstract]) OR (basaliom*[Title/Abstract])
3	(Basal[Title/Abstract] AND cell*[Title/Abstract]) OR (basocellular*[Title/Abstract] OR skin*[Title])
4	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab] OR Epithelioma*[tiab]
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
8	(#7) AND ("2015/06/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

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

2020-B-146

Kontaktdaten

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Arbeitsgemeinschaft für Dermatologische Onkologie (ADO) der DKG (Deutsche Krebsgesellschaft)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei "Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden."**? Wie sieht die Versorgungspraxis in Deutschland aus?**

Zusammenfassung

„Lokal-fortgeschrittene" Basalzellkarzinome (lfBCC) sind eine Untergruppe von Tumoren, die aufgrund ihrer Ausdehnung und insbesondere ihres destruierenden Tiefenwachstums eines interdisziplinären Therapiekonzepts bedürfen. Standard bei Patienten, die für eine kurative Operation oder eine Strahlentherapie nicht in Frage kommen, ist die systemische Therapie mit einem Hedgehog-Inhibitor. Bei Patienten mit Rezidiv oder Refraktärität keine zugelassene Therapieoption.

Behandlungsstandard bei Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden, ist Best Supportive Care.

Stand des Wissens

Unter „lokal-fortgeschrittenen" Basalzellkarzinomen (lfBCC) versteht man eine Untergruppe von Tumoren, die aufgrund ihrer Ausdehnung und insbesondere ihres destruierenden Tiefenwachstums eines interdisziplinären Therapiekonzepts bedürfen. Hierbei handelt es sich um Tumore, bei denen nach klinischer Diagnosestellung, erfolgter Primäroperation zur Diagnosesicherung oder ggf. erfolgloser Nachresektion und nach Einholung organ- bzw. fachspezifischer, insbesondere chirurgischer Expertise (interdisziplinäres Tumorboard) eine Komplettresektion (R0) nicht sicher erzielt werden kann, z.B. weil vital oder funktionell wichtige Strukturen betroffen sind.

Mit Vismodegib und Sonidegib sind zwei Inhibitoren des Hedgehog-Signalübertragungswegs für die Therapie von Patienten mit lokal fortgeschrittenem Basalzellkarzinom zugelassen, die für eine kurative Operation oder eine Strahlentherapie nicht in Frage kommen. Basis von Zulassung und Nutzenbewertung waren für Vismodegib zwei nicht-randomisierte Studien, bei Sonidegib eine randomisierte Studie zum Vergleich von zwei verschiedenen Dosierungen (200 vs 800 mg). Die Remissionsrate liegen bei 60-65%, das progressionsfreie Überleben bei 12-22 Monaten. Wesentliches Behandlungsziel bei diesen Patienten ist eine Rückbildung der belastenden, oft entstellenden Krankheitssymptome. Nebenwirkungen sind unter Hedgehog-Inhibitoren häufig.

Die Zahl der pro Jahr in Deutschland für die Therapie mit Hedgehog-Inhibitoren geschätzten

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Patientenzahlen wurde im Rahmen der frühen Nutzenbewertung auf 150 – 350 geschätzt.

Wenn also bereits eine systemische Therapie mit einem Hedghog-Inhibitor eingeleitet worden war, impliziert dies, dass alle lokalen Therapiemaßnahmen (OP, Strahlentherapie) sowie die Systemtherapie mit einem Hedgehog-Inhibitor ausgeschöpft worden sind und weiterer Therapiebedarf besteht.

Für diese Situation existiert derzeit keine zugelassene Therapieoption. Aufgrund der vielversprechenden Daten mit den Immuncheckpoint-Inhibitoren wird hier in den letzten Jahren zunehmend eine off-label Therapie mit in Erwägung gezogen werden.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden**“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Nein

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

2020-B-146

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 07.07.2020

Indikation gemäß Beratungsantrag

zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei "*Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden.*"**? Wie sieht die Versorgungspraxis in Deutschland aus?**

Einen Behandlungsstandard nach Versagen einer Hedgehog-Inhibitor Therapie gibt es nicht (1). Diese Patienten gelten bereits als nicht mehr sinnvoll operabel und bestrahlbar und es gibt keine zugelassenen Therapieoptionen. Chemotherapien können bei Basalzellkarzinomen zwar zu einem Ansprechen führen (Ansprechrate zwischen 20 und 60 %), bei allerdings nur sehr kurzer Ansprechdauer von 2–3 Monaten und ohne nachgewiesenen Effekt auf das Überleben (1). Erste publizierte Patientenfälle sowie eine erste klinische Studie mit 16 Patienten (2) zeigen eine Aktivität von PD-1-Antikörpern auch für diese Tumorentität. Eine aktuelle Studie mit insgesamt 130 Patienten in dieser Indikation hat alle Patienten rekrutiert, Ergebnisse liegen jedoch noch nicht vor (NCT03132636; EudraCT2016-003122-16; R2810-ONC-1620). Die aktuelle Versorgungspraxis ist anhand der Daten eine Krankenkassenanfrage zur Übernahme der Kosten für eine PD-1-Antikörpertherapie.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*Patienten mit lokal fortgeschrittenem oder metastasiertem Basalzellkarzinom (BCC), die zuvor mit einem Hedgehog-Inhibitor behandelt wurden***" die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Letztlich entscheidet der klinische Zustand des Patienten über die gewählte Therapie. Hier werden vor allem Tumorlast und ECOG berücksichtigt. Patienten mit weit fortgeschrittener Erkrankung werden palliativ betreut (Best Supportive Care), Patienten in gutem klinischen Zustand werden wenn möglich eine PD-1-Antikörpertherapie erhalten.

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