REVIEW ARTICLE

Update on Hedgehog Pathway Inhibitor Therapy for Patients with Basal Cell Naevus Syndrome or High-frequency Basal Cell Carcinoma

Babette J. A. VERKOUTEREN[1,2], Kelly A. E. SINX[1,2], Marie G. H. C. REINDERS[1,2], Maureen J. B. AARTS[2,3] and Klara MOSTERD[1,2]
[1]Department of Dermatology and [3]Department of Medical Oncology, Maastricht University Medical Center+ and [2]GROW School for Oncology and Development Biology, Maastricht University, Maastricht, The Netherlands

Some patients with basal cell carcinoma develop a large number of basal cell carcinomas during their lives. The most common underlying genetic disease that causes multiple basal cell carcinomas is basal cell naevus syndrome. Basal cell naevus syndrome is caused by a germline mutation in patched-1 (*PTCH1*), a tumour suppressor gene of the hedgehog signalling pathway. However, in a significant portion of patients with multiple basal cell carcinomas, no underlying genetic cause is found. Nevertheless, these patients can experience a treatment burden comparable to that of patients with basal cell naevus syndrome. They are referred to as high-frequency basal cell carcinoma patients. Hedgehog pathway inhibitors were the first group of targeted therapy for basal cell carcinomas. This study reviews the literature on hedgehog pathway inhibitor therapy for patients with basal cell naevus syndrome or high-frequency basal cell carcinoma, to provide an overview on efficacy, safety, dosing regimens, tumour resistance and reoccurrence, and health-related quality of life.

Key words: basal cell naevus syndrome; high-frequency; basal cell carcinoma; hedgehog pathway inhibitor; oral; topical.

Accepted May 10, 2022; Epub ahead of print May 10, 2022

Acta Derm Venereol 2022; 102: adv00741.

DOI: 10.2340/actadv.v102.980

Corr: Babette J. A. Verkouteren, Department of Dermatology, Maastricht University Medical Center+, P. Debyelaan 25, NL-6229 HX Maastricht, The Netherlands. E-mail: babette.verkouteren@mumc.nl

SIGNIFICANCE

This article provides an overview of all studies on hedgehog pathway inhibitor therapy for patients with high-frequency basal cell carcinomas or basal cell naevus syndrome, with an emphasis on efficacy, safety, dosing regimens, tumour resistance and reoccurrence, and quality of life during treatment. Evidence for treatment with hedgehog pathway inhibitors in patients with high-frequency basal cell carcinomas/basal cell naevus syndrome is scarce. Continuous treatment with oral hedgehog pathway inhibitors is effective, but it is often not suitable for long-term use due to adverse events. Clinical trial and real-world data show that personalized rotational schedules can be an effective and tolerable solution for a subset of patients.

A subset of patients with basal cell carcinoma (BCC) will develop a large number of BCCs during their lives. The most common genetic disease that causes multiple BCCs is basal cell naevus syndrome (BCNS), which has an estimated incidence in the range 1:31,000–1:256,000 (1, 2). In up to 85% of all patients with BCNS, a germline mutation in the tumour suppressor gene patched-1 (*PTCH1*), part of the hedgehog signalling pathway, is responsible (3). In a smaller proportion of patients with BCNS, a postyzygotic mutation in *PTCH1* or germline mutation in another hedgehog pathway gene, such as suppressor of fused (*SUFU*), can be found (3). In addition to BCNS, xeroderma pigmentosum, Bazex-Dupré-Christol and Rombo syndrome are also diseases with a susceptibility for developing multiple BCCs. In a subset of patients with multiple BCCs the underlying cause is unknown. These patients are referred to as high-frequency BCC (HF-BCC) patients, although there is no clear definition of the number and frequency of BCCs in patients with HF-BCC.

In general, BCCs in patients with BCNS and HF-BCC can be treated with local surgery (4, 5). However, there is an unmet need for new treatment options for patients with BCNS and HF-BCC. Some patients develop so many BCCs during their lives that surgical treatment can become physically challenging due to the large number of scars, but treatment also has a high emotional impact because of the burden of multiple hospital visits (6). The impact of multiple BCCs on health-related quality of life (HRQoL) can be substantial, as was found in a small cohort study of patients with BCNS (6). A treatment that could cure all lesions at the same time, with limited scarring and without major side-effects, is therefore highly desirable.

In 2012 the US Food and Drug Administration (FDA) approved the first oral hedgehog pathway inhibitor (HPI), vismodegib, for the treatment of advanced BCC (7). Its mechanism of action consists of inhibition of smoothened (SMO) and consequently inactivation of the hedgehog pathway. Unfortunately, tumour resistance, predominantly caused by *SMO* mutations, is a common problem in the treatment of advanced BCC with vismodegib (8, 9).

Vismodegib was the first HPI investigated in patients with HF-BCC and BCNS, but other types of oral HPIs have been investigated since. In general, side-effects, such as muscle spasms, alopecia and dysgeusia, eventually led to treatment discontinuation in the BCNS and HF-BCC population (10). However, patients have a lifelong indication for treatment and, in order to maintain long-term treatment, different dosing schedules are applied in clinical practice. Furthermore, topical HPIs have been developed for the treatment of multiple non-advanced BCCs. Although the mechanism of topical HPIs is the same, i.e. inhibition of SMO, the typical side-effects of oral HPIs are expected to be absent because of the local application and therefore minimal systemic effect.

The aim of this review is to outline the available clinical data for patients with BCNS and HF-BCC treated with any type or dosage of oral and topical HPIs.

MATERIALS AND METHODS

This systematic review, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was performed in the following 5 areas of interest: efficacy, safety, dosing regimen, tumour resistance and reoccurrence, and HRQoL in patients with BCNS and HF-BCC who were treated with HPI. Systematic reviews are exempted from institutional board review at Maastricht University Medical Center+.

First, a broad search was performed in clinicaltrials.gov, ISRCTN.org and clinicaltrialsregister.eu to determine which HPIs have been used for the treatment of BCCs. The following HPIs were identified: (*i*) oral: vismodegib/GDC-0449, sonidegib/LDE225, saridegib/IPI-926, itraconazole, BMS-833923, LEQ506 and TAK-441, and (*ii*) topical: patidegib/IPI-926, sonidegib/LDE225, and itraconazole. Multiple searches were performed using either "basal cell nevus syndrome/Gorlin syndrome", "high-frequency basal cell carcinoma", "multiple basal cell carcinoma" or "basal cell carcinoma" in combination with 1 of the HPIs, in order to identify suitable articles in clinicaltrials.gov, PubMed, and Embase from database inception to 17 September 2021.

One author (BV) performed the searches and independent review of the titles and abstracts. Studies describing treatment of patients with BCNS or HF-BCC with HPI monotherapy, which were relevant for the areas of interest, were selected for full article review. To assess efficacy and safety, all studies that reported outcomes on a group level were included, regardless of the outcome and safety measurements used. Furthermore, all case reports and series that described HPI monotherapy treatment of patients with BCNS or HF-BCC were evaluated for any information regarding dosing schedules, tumour resistance and reoccurrence and HR-QoL.

The following information was extracted: type and dosage of HPI, study design, level of evidence, treatment indication, number of participants, duration of treatment and follow-up, response criteria, efficacy, industry driven. Quality of evidence was assessed using Oxford Center for Evidence-Based Medicine levels. A list of common adverse events (AEs) and reasons for treatment discontinuation were also collected. Additional information on mutation analysis, resistance criteria, time to reoccurrence, and a brief summary was collected from tumour resistance and reoccurrence studies.

Additional information on type of questionnaire and time-points of its measurements was collected for HRQoL studies.

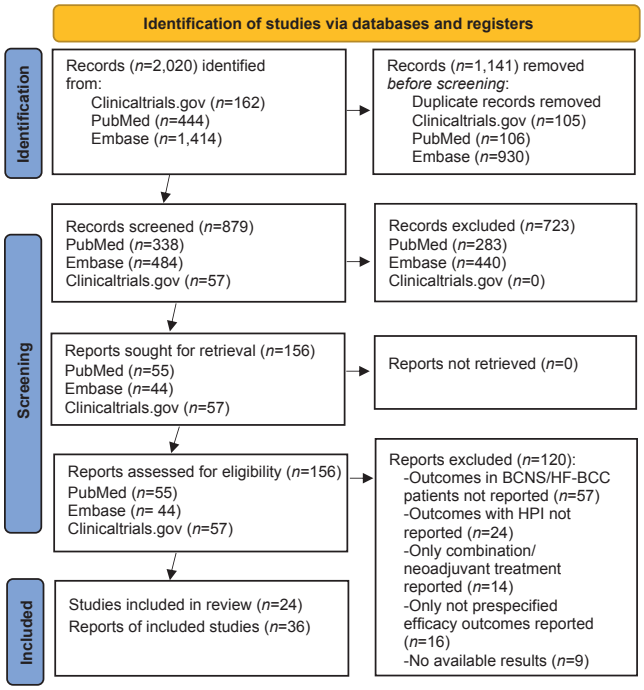

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-diagram. BCNS: basal cell naevus syndrome; HF-BCC: high-frequency basal cell carcinoma; HPI: hedgehog pathway inhibitor.

RESULTS

A total of 879 individual records were identified, of which 723 were removed after screening the titles and abstracts, and another 120 were removed after full-text review (**Fig. 1** and Appendix S1). A final total of 24 individual studies (36 different reports) were included, which discussed results on either efficacy ($n=8$), safety ($n=7$), dosing regimens ($n=8$), tumour resistance and reoccurrence ($n=15$), and/or HRQoL ($n=2$) in patients with BCNS and HF-BCC.

Efficacy results of all HPIs in all dosing schedules are shown in **Table I**.

Oral hedgehog pathway inhibitors

Continuous vismodegib. One randomized controlled trial (RCT), and 1 retrospective cohort reported outcomes for continuous vismodegib treatment (11–13). In the RCT, treatment with vismodegib 150 mg/day ($n=26$) compared with placebo ($n=15$) resulted in a mean rate of 2 new surgically eligible BCCs (SEBs) per year, compared with 34 in the placebo group. Furthermore, the vismodegib group showed a 65% reduction in mean size of existing SEBs (11, 12). A SEB was defined as clinically diagnosed BCC, regardless of subtype, of ≥ 5 mm diameter on the face or ≥ 9 mm on other body parts (no upper limit).

The retrospective cohort study determined progression-free survival in 16 patients with BCNS treated with vismodegib 150 mg daily and found a progression-free

Table I. Studies on hedgehog pathway inhibitors for basal cell naevus syndrome and high-frequency basal cell carcinoma patients

Study	HPI – dosing	Study type	Quality of evidence	Patient inclusion criteria	Response criteria	Total–BCNS patients	Randomization: *n*	Baseline tumours	Primary outcome	Secondary outcome
Tang et al. (11, 12)	Vismodegib 150 mg/day	Phase-2 double-blind RCT	1b	Clinical diagnosis of BCNS and ≥10 SEBs within last 2 years	Reduction in rate of nSEBs	41–41	Vismodegib: 26 Placebo: 15	Mean number nSEBs *at baseline*: 44 37	Mean rate nSEBs/year at *month 3*: 2 34; $p<0.0001$	Change in size of *existing SEBs*: –60 mm +55 mm; $p<0.0001$
Lear et al. (14)	Sonidegib 400 mg/day	Phase-2 double-blind RCT	1b	Clinical diagnosis of BCNS and ≥2 BCCs	Clearance rate of main target BCC	10–10	LDE225: 8 Placebo: 2	Total BCCs at baseline: 566 510	Clinical clearance *rate at week 16*: 100%: 3 76–99%: 3 26–25%: 1 1–25%: 1 worsening: 1	BCC tumour count at *week 16*: 309 619
Dreno et al. (15)	Vismodegib 150 mg alternated with placebo	Phase-2 double-blind RCT*	1b	Patients with ≥6 BCCs	Mean relative reduction in number of BCCs	229–85	Group A: 116 Group B: 113	Mean number of BCCs *at baseline*: 9.8 9.1	Mean reduction at *week 73*: 55.2% 56.6%; $p=0.21$	Mean reduction 3 target *BCCs at week 73*: 82.9% 68.8%; $p=0.02$
Verkouteren et al. (13)	Vismodegib 150 mg/day	Retrospective cohort study	4	Clinical diagnosis of BCNS	Progression-free survival and response rate	24–19	Not applicable	Unknown	Median *progression-free survival:* 19.1 months (95% CI 7.4–20.2)	Probability of PR within *3 months*: 93.3% (95% CI 74.0–99.6)
Sohn et al. (22)	Itraconazole 0.7% gel twice daily	Phase-2 open-label intrapatient	3b	Patients with >3 BCCs annually	Change in BCC tumour area	9–6	Itraconazole: 9 Vehicle: 9	*Total BCCs treated*: 65 42	*Change at week 4*: 0.04% –10.9%; $p=0.40$	*Change at week 12*: 8.9% 26.5%; $p=0.40$
Epstein et al. (23)	Patidegib 2% and 4% gel twice daily	Phase-2 double-blind parallel assignment	1b	Clinical diagnosis of BCNS and ≥10 BCCs within last 2 years	Change in BCC size	17–17	Patidegib 2%: 6 Patidegib 4%: 6 Vehicle: 5	Total number of SEBs *at baseline*: 21 24 16	Decrease in SEB *size at week 26*: 51.3%; ($p=0.03$) 26.6%; ($p=0.76$) 21.8%	Mean number nSEBs *at week 26*: 0.4 (2% and 4%) 1.4; $p=0.048$
Skvara et al. (19, 24)	Sonidegib 0.25% and 0.75% cream twice daily	Phase-2 double-blind, 2 parts, parallel assignment^	1b	Clinical diagnosis of BCNS with BCCs on 2 different body parts	Percentage of BCCs with clearance	18–18	Part 1–4 weeks Vehicle: 8 LDE225 0.75%: 8 Part 2–6 weeks LDE225 0.25%: 3 LDE225 0.75%: 7	Total number of BCCs *at baseline*: 14 13 12 22	BCCs with partial/complete *clearance at week 4*: 7%/0% 92%/23% 83%/0% 77%/0%	Mean change in 3D tumour size *at week 4*: 7.0 –35.3% –19.3% –43.4%

*Consisted of 2 groups; group A: 12 weeks vismodegib 150 mg/day – 8 weeks placebo alternately, group B: 24 weeks vismodegib 150 mg/day followed by 8 weeks placebo – 8 weeks vismodegib 150 mg alternately. ^Part 1: participants were exposed to both topically applied 0.75% LDE225 cream and LDE225 vehicle cream twice daily for 28 days where each treatment was randomized to 2 different test areas on each participant, part 2: participants were exposed to topically applied 0.25% or 0.75% LDE225 cream twice daily for 6 weeks or 0.75% LDE225 cream twice daily for 9 weeks. +Using a 6-point scale (worsening, no change, 1–25%, 26–75%, 76–99% or 100% improvement).
HPI: hedgehog pathway inhibitor; RCT: randomized controlled trial; BCC: basal cell carcinoma; SEB: surgically eligible basal cell carcinoma; nSEB: new surgically eligible basal cell carcinoma (SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face); RR: relative reduction; PR: partial response; 95% CI: 95% confidence interval.

survival of 19.1 months (95% confidence interval (95% CI) 7.4–20.2) (13). Probability of partial response within 3 months after treatment was 93.3% (95% CI 74.0–99.6).

Continuous sonidegib. Only one randomized placebo-controlled trial reported on continuous sonidegib treatment in 9 patients with BCNS (14). Treatment with sonidegib 400 mg daily ($n=7$) resulted in a 100% target BCC clinical clearance rate in 3 patients, 76–99% in 3 others, and 26–75% in 1 patient. In the placebo group ($n=2$), 1 patient had a 1–25% clinical clearance rate and the target BCC of 1 patient showed worsening (14). The total number of BCCs decreased from 566 at baseline to 309 at week 16 in the sonidegib and increased from 510 at baseline to 619 at week 16 in the placebo group. The numbers were too small for statistical analysis.

Dosing regimens for oral HPIs. One RCT determined the efficacy of 2 vismodegib regimens in 85 patients with BCNS and 144 patients with HF-BCC (15). Group A received 12 weeks of vismodegib 150 mg/day alternated with 8 weeks of placebo and group B received 24 weeks of vismodegib 150 mg/day followed by 8 weeks of vismodegib 150 mg/day alternated with 8 weeks of placebo. At week 73, the mean relative reduction of the number of clinical BCCs was 62.7% in group A compared with 54.0% in group B ($p=0.21$). Furthermore, of all 34 case reports/series/cohorts about HPIs in HF-BCC/BCNS patients that were found in the literature search, 9 reported on dosing regimens (13, 15–21). All but one of these reports concerned different dosing for vismodegib. Most schedules were based on several weeks/months on and off treatment ($n=25$ patients), but also every other day ($n=4$ patients) and Monday–Friday dosing ($n=2$ patients) schedules have been used. Overall, outcomes were badly reported and too heterogeneous for effective comparison between different schedules. Results are summarized in **Table II**.

Table II. Overview of studies reporting dosing schedules and outcomes

Study	Patients/schedule	Outcome
Verkouteren et al. 2020 (13)	12/19 patients with BCNS received ≥2 treatment sequences (restart after break >8 weeks) with a maximum of 4 sequences in 6 years 1 HF-BCC patient: 3 months on and off treatment	All patients responded to vismodegib in all following sequences "Successfully" >3 years
Villani et al. 2020 (21)	7 patients with HF-BCC 1: 20 weeks on, 12 weeks off and on treatment 2: 16 weeks on, 8 weeks off and 12 weeks on treatment 3: 12 weeks on and off treatment 4: 8 weeks on and off treatment 5: once every second day for 16 months 6: once every second day for 22 months 7: once every second day for 16 months	Not reported
Tronconi et al. 2020 (20)	4/8 patients with multiple BCC/Gorlin changed from daily to 4 weeks on and 2 weeks off treatment	All patients had complete response after a total treatment duration of 27.3 months (95% CI 11.7–38.8)
Valenzuela-Onate et al. 2020 (17)	3 patients with BCNS Patient 1: 3 months on and off treatment Patient 2: Monday–Friday dosing Patient 3: Monday–Friday dosing	No new BCCs after 6 months No new BCCs after 9 months, 11/14 BCC: CR, 3/14: PR Size reduction >30% after 3 months
Yang et al. 2016 (16)	2 patients with BCNS Patient 1: 1 month on and 2 months off treatment Patient 2: 2 months on and off treatment	Biopsy-detected BCC in years (4-3-2-1) before/after (1–2) treatment: 12-11-15-9/2-1 4-1-4-5/1
Hoffmann et al. 2021 (19)	HF-BCC patient with >100 BCCs and sonidegib 200 mg once every day	Clinical remission of all but 1 BCC after 9 months
Mendes et al. (18)	BCNS patient on and off treatment for >3 years (reintroduction after recurrence and discontinuation after complete response)	"Well controlled"

All patients were treated with vismodegib unless stated otherwise.
BCC: basal cell carcinoma; 95% CI: 95% confidence interval; BCNS: basal cell naevus syndrome; HF-BCC: high-frequency basal cell carcinoma; CR: complete response; PR: partial response.

Topical hedgehog pathway inhibitor

Three randomized-vehicle-controlled phase-2 trials investigating twice daily application of topical HPIs were registered at clinicalrials.gov (19, 22–24).

The first study compared itraconazole 0.7% gel for 47 BCCs with vehicle for 25 BCCs within the same 9 patients (6 patients with BCNS and 3 patients with HF-BCC) (22). Four target lesions were identified at baseline and at least 1 was treated with placebo according to the study protocol. The change in tumour area was +0.04% in the itraconazole-treated BCCs compared with –10.9% in the vehicle-treated BCCs after 4 weeks compared with baseline. After 12 weeks the change in tumour area was +8.9% in the itraconazole and +26.5% in the vehicle BCCs.

The second trial compared patidegib 2%, 4% and vehicle gel in BCCs >5 mm at baseline in 16 patients with BCNS, randomized in a 1:1:1 ratio (23). After 26 weeks of application, the tumour size decreased by 51.3% in 21 BCCs the patidegib 2% group ($n=6$ patients), 26.6% in

Table III. Prevalence of side-effects with oral hedgehog pathway inhibitors

	Tang et al. (11, 12)	Lear et al. (14)	Dreno et al. (15) Group A*	Dreno et al. (15) group B*
Hedgehog pathway inhibitor	Vismodegib	Sonidegib	Vismodegib	Vismodegib
Dosage	150 mg daily	400 mg daily	150 mg daily alternated with placebo	150 mg daily alternated with placebo
Treatment duration	Unknown, 10 patients were treated for more than 15 months continuously	16 weeks	71.6 weeks	68.4 weeks
Patients available for safety results	40	8	114	113
Alopecia	100% (40)	25% (2)	63% (72)	65% (73)
Muscle spasms	100% (40)	38% (3)	73% (83)	83% (93)
Dysgeusia	93% (37)	13% (1)	66% (75)	67% (75)
Weight decreased	78% (31)	NM	21% (24)	19% (21)
Gastrointestinal upset/diarrhoea	65% (26)	13% (1)	18% (20)	16% (18)
Fatigue	48% (19)	25% (2)	21% (24)	23% (26)
Nausea	10% (4)	25% (2)	20% (23)	13% (15)
Runny nose/ nasopharyngitis	18% (7)	25% (2)	NM	NM
Common cold/asthenia	20% (8)	NM	13% (15)	18% (20)
Headache	NM	25% (2)	10% (11)	11% (12)
Treatment discontinuation/interruption	21/40 within 18 months	2/8 within 16 weeks	50/116 within 73 weeks	57/113 within 73 weeks
Reason for treatment discontinuation				
AE/laboratory abnormalities	30% (12)	25% (2)	20% (23)	27% (30)
Patients decision/refused treatment	NM	NM	6% (7)	3% (3)
Patient satisfaction	3% (1)	NM	NM	NM
Site method	15% (6)	NM	NM	NM
Withdrew consent	NM	NM	10% (12)	12% (13)
Investigators decision	NM	NM	2% (2)	5% (6)
Disease progression	NM	NM	3% (3)	3% (3)
Died	5% (2)	NM	NM	NM

*Group A: 12 weeks vismodegib 150 mg/day – 8 weeks placebo alternately, group B: 24 weeks vismodegib 150 mg/day followed by 8 weeks placebo – 8 weeks vismodegib 150 mg alternately.
AE: adverse event; NM: not mentioned.

24 BCCs in the patidegib 4% group ($n=6$ patients) and 21.8% in 16 BCCs in the vehicle group ($n=4$ patients). In the third trial, LDE225 0.75% cream on 13 BCCs was compared with vehicle on 14 BCCs within the same 8 patients with BCNS (24). The mean decrease in 2D tumour size, was 38.4% after 4 weeks of treatment in the LDE225 0.75% group, compared with an increase of 9.6% in the placebo group. In part 2 of the trial, LDE225 0.75% cream in 7 patients was compared with LDE225 0.25% cream in 3 patients and showed a mean decrease in 2D tumour size of 28.5% and 36.3%, respectively, after 6 weeks of treatment (19).

Safety

The most commonly reported AEs and reasons for treatment discontinuation of oral HPIs are shown in **Table III**.

Oral hedgehog pathway inhibitors. In a trial by Tang et al., 40 patients were eventually treated with vismodegib. Thirty-one patients (77.5%) needed a temporary or permanent treatment discontinuation due to AEs during a 36-month study period (11, 12).

Dreno et al. (15) found that intermittent dosing of vismodegib led to treatment discontinuation because of AEs in 23/116 (19.8%) patients in group A and 30/113 (26.5%) patients in group B. The regimen in group A was associated with fewer severe treatment-related AEs compared with group B. The median duration of treatment was 71.6 weeks and 68.4 weeks in group A and B, respectively. Treatment with continuous sonidegib led to treatment discontinuation in 2 (25%) out of 8 patients due to AEs during 16 weeks of treatment (14).

Topical hedgehog pathway inhibitor. All 3 topical HPIs were applied twice daily on several BCCs within a single patient. Itraconazole 0.7% gel for 4 weeks caused application site reaction and pruritus in 4/9, lesion pain in 3/9, and xerosis and dysgeusia in 1/9 patients (**Table IV**) (22).

Patidegib 4% gel led to application site alopecia, dermatitis, pain and rash in 1/6 patients during 26 weeks of treatment (23). None of these AEs occurred in the 6 patients treated with patidegib 2% gel. In part I of the topical LDE225 trial, 4/8 patients reported local skin irritation and 1/8 reported skin fissures, it is not known if this happened following application with placebo or LDE225 0.75% (24). Urticaria and increased hepatic enzyme activity in blood investigations were seen in 1/8 patients. In part II, 1/7 patients treated with LDE225 0.75% cream reported local skin irritation and urticaria. None of these AEs occurred in the 3 patients treated with LDE225 0.25% cream (19). It is not known if any of the AEs led to treatment discontinuation in the 3 trials describing topical HPI treatment.

Tumour resistance and reoccurrence

After eligibility assessment of the previously described RCTs, cohort studies and 34 case reports/series, information on resistance/reoccurrence was found in 15 different studies (11–13, 17–19, 25–34). Development of resistance during treatment with an oral HPI was reported in 9 articles and tumour reoccurrence after treatment discontinuation was also reported in 9 articles (**Table V**). Only 1 article reported reoccurrence in a patient treated with sonidegib, all other concerned resistance/reoccurrence in vismodegib. No information on tumour reoccurrence after topical HPIs was found, but, as was described in the efficacy section, not all BCCs responded to topical HPI treatment, which might be caused by primary resistance.

Health-related quality of life

Only Dreno et al. measured HRQoL, in a study of 229 patients using a validated questionnaire (15). The Skindex-16, which comprises 3 domains (symptoms, emotions and function) was measured 8 times between

Table IV. Prevalence of side-effects with topical hedgehog pathway inhibitors (HPIs)

	Skvara et al. (24)			Epstein et al. (23)			Sohn et al. (37)
Side-effects	Part I LDE225 0.75% & vehicle $n=8$	Part II LDE225 0.25% $n=3$	Part II LDE225 0.75% $n=7$	Patidegib 2% $n=6$	Patidegib 4% $n=6$	Vehicle $n=5$	Itraconazole 0.7% & vehicle* $n=9$
SAE	0 (0%)	0 (0%)	1 (14%) Hepatic enzyme increased	0 (0%)	0 (0%)	1 (20%) Pneumonia	0 (0%)
Skin fissures	1 (13%)	0 (0%)	0 (0%)	–	–	–	–
Skin irritation	4 (50%)	0 (0%)	1 (14%)	–	–	–	–
Urticaria	0 (0%)	0 (0%)	1 (14%)	–	–	–	–
Application site alopecia	–	–	–	0 (0%)	1 (17%)	0 (0%)	–
Application site dermatitis	–	–	–	0 (0%)	1 (17%)	0 (0%)	–
Application site pain	–	–	–	0 (0%)	1 (17%)	0 (0%)	–
Application site rash	–	–	–	0 (0%)	1 (17%)	0 (0%)	–
Application site reaction	–	–	–	0 (0%)	0 (0%)	1 (20%)	4 (44%)
Alopecia	–	–	–	0 (0%)	0 (0%)	1 (20%)	–
Abnormal hair growth	–	–	–	1 (17%)	0 (0%)	0 (0%)	–
Pruritus	–	–	–	0 (0%)	0 (0%)	1 (20%)	4 (44%)
Rash	–	–	–	0 (0%)	1 (17%)	0 (0%)	–
Lesion pain	–	–	–	–	–	–	1 (11%)

*Adverse effect in itraconazole 0.7% gel patients resolved after the end of the trial except in 2 patients who had persistent mild lesion pain, pruritus and xerosis cutis.
SAE: severe adverse effect.

Table V. Resistance and reoccurrence

Study	Study type – quality of evidence	Patients, *n* (BCNS/ HF-BCC)	BCCs described, *n*	Resistance during vismodegib treatment, primary or secondary	*(Re)occurrence* after discontinuing vismodegib treatment
Tang et al. (11, 12)	Phase-2 double-blind RCT (placebo) – 1b	41 – BCNS	>2,000	During vismodegib treatment: – Two pre-existing BCCs did not respond – Mutational profile: 1 had a vismodegib-resistant *SMO* mutation (Val231Met) No information on secondary resistance described	– During treatment breaks BCC reoccurred, no exact number or percentage was provided
Chang & Oro (25)	Retrospective cohort – 2	3	133	During vismodegib treatment: – After a mean period of 55.3 weeks – 6 out of 133 BCCs regrew	Not described
Sinx et al. (26)	Case report – 5	1 – BCNS	>3	During 3 years vismodegib treatment: – 2 BCCs regrew after initial complete response – Mutational profile: both had vismodegib-resistant *SMO* mutations (Ser241Phe and Asp473Asn)	– Two months after discontinuing 3 years vismodegib treatment, BCCs reoccurred at their pre-treatment locations. – Number unknown
Banvolgyi et al. (27)	Retrospective cohort – 5	4	Unknown	Not described	– Three months after discontinuing 4 years vismodegib treatment, BCCs reappeared in 1 patient
Valenzuela-Onate et al. (17)	Case series – 5	3	5	Not described	– In 3 cases, at least 19 BCCs developed within 2 years after discontinuing vismodegib of unknown treatment duration.
Wolfe et al. (28)	Case report – 5	1	19	Not described	– Two years after discontinuing 7 months vismodegib treatment, 10 out of 19 BCCs on the head & neck reoccurred
Verkouteren et al. (13)	Retrospective cohort – 5	24 – 19 BCNS and 5 HF-BCC	Unknown	5/24 patients had progressive disease during vismodegib 150 mg/daily treatment	In 17/24 patients progressive disease was seen after vismodegib discontinuation
Tauber et al. (29)	Cohort – 5	8 – HF-BCC (4 or more BCCs)	53	In 1 patient with 7 BCCs, new BCCs developed after reduction of vismodegib 150 mg daily to an unknown reduced dose. BCCs regressed after increasing the dose to 150 mg daily	Not described
Kirkpatrick et al. (30)	Case report – 5	1 – BCNS	Unknown	After 36 months of vismodegib 150 mg/daily 1 new BCC had developed	Not described
Soura et al. (31)	Case report – 5	1 – BCNS	79	– After 12 months of vismodegib 150 mg/daily: 1/79 BCCs partially responded, 78/79 complete response – After 30 months of vismodegib: Remaining BCC increased in size and 2 BCCs reoccurred	Not described
Piccerillo et al. (32)	Case report – 5	1 – BCNS	>50	Not described	– 36 months after discontinuing 6 months vismodegib 150 mg daily treatment, relapse of all previously treated BCCs was seen
Van Eecke et al. (33)	Case report – 5	1 – BCNS	Multiple	Not described	– Two months after discontinuing 24 months of vismodegib treatment (dose not mentioned), regrowth of BCCs was seen.
Kesireddy et al. (34)	Case report – 5	1 – BCNS	Multiple	– After 11 months of vismodegib 150 mg daily pre-existing BCCs increased and new BCCs developed but continued for another 18 months of vismodegib during which 22 BCCs developed	Not described
Hoffmann et al. (19)	Case report – 5	1 – HF-BCC	>100	– After sonidegib 200 mg every second day for 9 months only 1 BCC remained for which no therapy was initiated (patient desire)	Not described
Mendes et al. (18)	Case report – 5	1 – BCNS	High count	Not described	– Patient received vismodegib, (dose not mentioned) in on-off regimen for >3 years. Vismodegib is reintroduced after recurrence of BCCs.

RCT: randomized control trial; BCNS: basal cell naevus syndrome; BCC: basal cell carcinoma; HF-BCC: high-frequency BCC.

baseline and end-of-treatment (week 73), and at 12, 24 and 52 weeks follow-up (35). Outcomes ranged from 0 (never bothered) to 100 (always bothered). Both alternating treatment regimens with vismodegib showed a decrease of ≥10 points from baseline to week 9 and every point post-baseline in all domains, which was considered to be a clinical meaningful improvement (36). A decrease in HRQoL was seen in all domains after discontinuation of treatment, but HRQoL scores had not returned to baseline scores 52 weeks after discontinuation of treatment.

Furthermore, Tang et al. reported that 23/41 included patients with BCNS responded to a telephone questionnaire evaluating vismodegib treatment at some time-point after the end of the trial. Of those 23 patients, 18 stated that they preferred treatment with vismodegib over surgery (11, 12).

DISCUSSION

After reviewing all literature on oral and topical HPI therapy in patients with BCNS and HF-BCC, we conclude that high-quality evidence for HPI treatment in this population is scarce. Both continuous vismodegib and sonidegib and alternating vismodegib have been proven effective in patients with BCNS. No head-to-head trial comparing vismodegib and sonidegib treatment have

been performed, and the reviewed trials are too heterogeneous to compare.

During continuous oral HPI treatment, AEs are very common, and are often the reason for discontinuation of treatment. The reported percentage of patients that interrupt or cease treatment due to AEs is 25–77.5% (12, 14). This range is broad, and variation may partly be caused by various other reasons reported for treatment cessation, such as "patient's decision", "withdrawal of consent", or "refusing of treatment". Furthermore, it is not clear from the studies which AEs at which grades caused treatment discontinuation. After treatment discontinuation, at least part of the BCCs will recur, but there appears to be a broad range of time to tumour recurrence.

In the continuous vismodegib trial, 77.5% of subjects interrupted treatment for ≥2 months. Intermittent dosing alternating several weeks of oral HPI with no treatment has been proposed as a strategy for better toleration of the AEs. In the 1 RCT investigating the efficacy of intermittent vismodegib by Dreno et al. (15), alternating 12 weeks of treatment with 8 weeks of placebo appeared to be more effective compared with 8 weeks on and off treatment, and was associated with fewer severe treatment-related AEs. Only a few other articles report on alternating dosing schedules and most of them investigated similar dosing strategies to those reported by Dreno et al. (15) However, in 4 patients a daily alternating schedule was reported and in 2 patients investigators opted for a Monday–Friday dosing. These dosing schedules also appear to be effective, but the level of evidence is low.

Topical HPIs have been developed to avoid AEs in patients requiring long-term treatment for multiple BCCs. From the 3 reported phase-2 trials on 3 different HPIs, it can be concluded that the effectiveness varies per active pharmaceutical ingredient. Although the trials could not be compared due to heterogeneity in population and outcome measurements, topical itraconazole 0.7% gel application for 4 weeks appeared not to be effective in 9 patients and topical patidegib 2% and LDE225 0.75% was investigated in 17 and 8 patients, respectively, showing more promising results. A follow-up phase 3 RCT with LDE225 0.75% cream was withdrawn before participants were enrolled. Although a follow-up phase 3 RCT comparing patidegib 2% gel with vehicle was completed recently, results are not yet available and the following open-label extension study was terminated due to low blinded event rate according to clinicaltrials.gov.

In conclusion, evidence for treatment with HPIs in patients with HF-BCC and BCNS is scarce. Continuous treatment with oral HPIs is effective, but they are often not suitable for long-term use, due to adverse events. Personalized rotational schedules for oral HPIs can be an effective and tolerable solution for a subset of patients with BCNS and HF-BCC. Topical HPIs appear to be promising, as they are accompanied by fewer AEs, but efficacy and safety data to support approval are not expected to be available in the short term.

Conflicts of interest: BJAV, MGHCR and KM are local investigators of the Pelle-926-301 and Pelle-926-301E trials. KM participated in an input session regarding treatment of patients with Gorlin syndrome organized by LEO Pharma.

REFERENCES

1. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010; 152A: 327–332.
2. Lo Muzio L, Nocini PF, Savoia A, Consolo U, Procaccini M, Zelante L, et al. Nevoid basal cell carcinoma syndrome. Clinical findings in 37 Italian affected individuals. Clin Genet 1999; 55: 34–40.
3. Verkouteren BJA, Cosgun B, Reinders M, Kessler P, Vermeulen RJ, Klaassens M, et al. A guideline for the clinical management of basal cell nevus syndrome (Gorlin-Goltz syndrome). Br J Dermatol 2022; 186: 215–226.
4. Peris K, Fargnoli MC, Garbe C, Kaufmann R, Bastholt L, Seguin NB, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer 2019; 118: 10–34.
5. Work G, Invited R, Kim JYS, Kozlow JH, Mittal B, Moyer J, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol 2018; 78: 540–559.
6. Huq AJ, Bogwitz M, Gorelik A, Winship IM, White SM, Trainer AH. Cohort study of Gorlin syndrome with emphasis on standardised phenotyping and quality of life assessment. Intern Med J 2017; 47: 664–673.
7. Axelson M, Liu K, Jiang X, He K, Wang J, Zhao H, et al. U.S. Food and Drug Administration approval: vismodegib for recurrent, locally advanced, or metastatic basal cell carcinoma. Clin Cancer Res 2013; 19: 2289–2293.
8. Atwood SX, Sarin KY, Whitson RJ, Li JR, Kim G, Rezaee M, et al. Smoothened variants explain the majority of drug resistance in basal cell carcinoma. Cancer Cell 2015; 27: 342–353.
9. Sharpe HJ, Pau G, Dijkgraaf GJ, Basset-Seguin N, Modrusan Z, Januario T, et al. Genomic analysis of smoothened inhibitor resistance in basal cell carcinoma. Cancer Cell 2015; 27: 327–341.
10. Basset-Seguin N, Hauschild A, Grob JJ, Kunstfeld R, Dreno B, Mortier L, et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. Lancet Oncol 2015; 16: 729–736.
11. Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 2012; 366: 2180–2188.
12. Tang JY, Ally MS, Chanana AM, Mackay-Wiggan JM, Aszterbaum M, Lindgren JA, et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016; 17: 1720–1731.
13. Verkouteren BJA, Wakkee M, Reyners AKL, Nelemans P, Aarts MJB, Racz E, et al. Eight years of experience with vismodegib for advanced and multiple basal cell carcinoma patients in the Netherlands: a retrospective cohort study. Br J Cancer 2021; 124: 1199–1206.
14. Lear JT, Hauschild A, Stockfleth E, Squittieri N, Basset-Seguin N, Dummer R. Efficacy and safety of sonidegib in adult patients with nevoid basal cell carcinoma syndrome (Gorlin Syndrome): results from a Phase 2, double-blind, randomized trial. Clin Cosmet Investig Dermatol 2020; 13: 117–121.
15. Dreno B, Kunstfeld R, Hauschild A, Fosko S, Zloty D, Labeille B, et al. Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a

randomised, regimen-controlled, double-blind, phase 2 trial. Lancet Oncol 2017; 18: 404–412.
16. Yang X, Dinehart SM. Intermittent vismodegib therapy in basal cell nevus syndrome. JAMA Dermatol 2016; 152: 223–224.
17. Valenzuela-Onate CA, Magdaleno-Tapial J, Garcia-Legaz Martinez M, Perez-Pastor G, Sanchez Carazo JL. Drug holiday approach for Vismodegib treatment in patients with nevoid basal cell carcinoma syndrome: three cases from real clinical practice. Dermatol Ther 2020: 33: e13540.
18. Mendes SR, Brinca A, Vieira R. Vismodegib hedgehog-signaling inhibition and treatment of basal cell carcinomas in gorlin-goltz syndrome. Available from https://www.wcd-2019milan-dl.org/abstract-book/documents/abstracts/39-skin-cancer/vismodegib-hedgehog-signaling-inhibition-and-5398.pdf.
19. Hoffmann V, Husak R, Maiwirth F, Sasama B, Zahn A, Guski S, et al. Sonidegib in a patient with multiple basal cell carcinomas and HIV infection. J Dtsch Dermatol Ges 2021; 19: 592–594.
20. Tronconi MC, Solferino A, Giordano L, Borroni R, Mancini L, Santoro A. Tailored toxicity-driven administration of vismodegib in patients with multiple or locally advanced basal cell carcinoma: a pilot analysis. Front Oncol 2020; 10: 563404.
21. Villani A, Costa C, Fabbrocini G, Scalvenzi M. Drug holiday regimen for vismodegib treatment in patients with multiple primary basal cell carcinomas. Dermatol Ther 2020; 33: e13707.
22. Sohn GK, Kwon GP, Bailey-Healy I, Mirza A, Sarin K, Oro A, et al. Topical itraconazole for the treatment of basal cell carcinoma in patients with basal cell nevus syndrome or high-frequency basal cell carcinomas: a Phase 2, open-label, placebo-controlled trial. JAMA Dermatol 2019; 155: 1078–1080.
23. Epstein EH, Lear JT, Saldanha G, Tang JY, Harwoord C. Hedgehog pathway inhibition by topical patidegib to reduce BCC burden in patients with basal cell nevus (Gorlin) syndrome. J Clin Oncol 2018; 36: 15_suppl.
24. Skvara H, Kalthoff F, Meingassner JG, Wolff-Winiski B, Aschauer H, Kelleher JF, et al. Topical treatment of basal cell carcinomas in nevoid basal cell carcinoma syndrome with a smoothened inhibitor. J Invest Dermatol 2011; 131: 1735–1744.
25. Chang AL, Oro AE. Initial assessment of tumor regrowth after vismodegib in advanced basal cell carcinoma. Arch Dermatol 2012; 148: 1324–1325.
26. Sinx KAE, Roemen G, van Zutven V, Janssen R, Speel EM, Steijlen PM, et al. Vismodegib-resistant basal cell carcinomas in basal cell nevus syndrome: clinical approach and genetic analysis. JAAD Case Rep 2018; 4: 408–411.
27. Banvolgyi A, Anker P, Lorincz K, Kiss N, Marton D, Fesus L, et al. Smoothened receptor inhibitor vismodegib for the treatment of basal cell carcinoma: a retrospective analysis of efficacy and side effects. J Dermatolog Treat 2020; 31: 387–398.
28. Wolfe CM, Green WH, Cognetta AB, Jr., Hatfield HK. Basal cell carcinoma rebound after cessation of vismodegib in a nevoid basal cell carcinoma syndrome patient. Dermatol Surg 2012; 38: 1863–1866.
29. Tauber G, Pavlovsky L, Fenig E, Hodak E. Vismodegib for radiation-induced multiple basal cell carcinomas (BCCs) of the scalp. J Am Acad Dermatol 2015; 73: 799–801.
30. Kirkpatrick E, Dobriansky D, Scurry J. Gorlin syndrome, vulvar basal cell carcinomas, vismodegib, and lichen sclerosus: from the ISSVD Case Consultation Committee. J Low Genit Tract Dis 2016; 20: e40–e41.
31. Soura E, Plaka M, Dessinioti C, Syrigos K, Stratigos AJ. Can hair re-growth be considered an early clinical marker of treatment resistance to Hedgehog inhibitors in patients with advanced basal cell carcinoma? A report of two cases. J Eur Acad Dermatol Venereol 2016; 30: 1726–1729.
32. Piccerillo A, Di Stefani A, Costantini A, Peris K. Sonidegib after vismodegib discontinuation in a patient with Gorlin-Goltz syndrome and multiple basal cell carcinomas. Dermatol Ther 2021; 34: e15095.
33. Van Eecke L, Wolter P, Bechter O, Rogiers A, De Smedt J, Garmyn M. P129: Long-term follow-up of two patients with nevoid basal cell carcinoma syndrome (NBCCS) treated with vismodegib. Melanoma Res 2016; 26: e75–e76.
34. Kesireddy M, Mendiola VL, Jana B, Patel S. Long-term response to vismodegib in a patient with Gorlin-Goltz syndrome: a case report and review of pathological mechanisms involved. Cureus 2019; 11: e5383.
35. Schadendorf D, Hauschild A, Fosko S, Zloty D, Labeille B, Grob JJ, et al. Quality-of-life analysis with intermittent vismodegib regimens in patients with multiple basal cell carcinomas: patient-reported outcomes from the MIKIE study. J Eur Acad Dermatol Venereol 2020; 34: e526–e529.
36. Chren MM, Sahay AP, Bertenthal DS, Sen S, Landefeld CS. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol 2007; 127: 1351–1357.
37. Sohn GK, Kwon GP, Bailey-Healy I, Mirza A, Sarin K, Oro A, et al. Topical itraconazole for the treatment of basal cell carcinoma in patients with basal cell nevus syndrome or high-frequency basal cell carcinomas: a Phase 2, open-label, placebo-controlled trial. JAMA Dermatol 2019; 155: 1078–1080.