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

Babette J. A. VERKOUTEREN1,2, Kelly A. E. SINX1,2, Marie G. H. C. REINDERS1,2, Maureen J. B. AARTS2,3 and Klara MOSTERD1,2
1Department of Dermatology and 2Department of Medical Oncology, Maastricht University Medical Center+ and 3GROW School for Oncology and Development Biology, Maastricht University, Maastricht, The Netherlands

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 postzygotic 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, dosage 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, ISR-CTN.org and clinicaltrialregister.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, irtraconazole, BMS-833923, LEQ056 and TAK-441, and (ii) topical: patidegib/IPI-926, sonidegib/LDE225, and irtraconazole. 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.

**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 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...
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 alternating 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 alternating 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 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.     | Vismodegib 150 mg/day | Phase-2 double-blind RCT | 1b                  | Clinical diagnosis of BCNS and ≥10 BCCs | Reduction in rate of nSEBs | Vismodegib: 26 Placebo: 15 | Mean number of nSEBs at baseline: 30 | Placebo: 15 | Mean rate nSEBs/year at month 3 | Change in rate of existing SEBs: -60 mm; +55 mm |
| Lear et al.     | Sonidegib 400 mg/day | Phase-2 double-blind RCT | 1b                  | Clinical diagnosis of BCNS and ≥2 BCCs | Clearance rate of main target BCC | LDE225: 8 Placebo: 2 | Total BCCs at baseline: 566 | Placebo: 2 | Clinical clearance rate at week 16 | 76–99.9%: 3 26–25%: 1 1–25%: 1 100%: 3 |
| Dreno et al.    | Vismodegib 150 mg/day 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: 10.8 | Unknown | Mean reduction at week 73: 55.2% | Mean reduction 3 target BCCs at week 73: 18.9% |
| Verkouteren et al. (13) | Vismodegib 150 mg/day | Retrospective cohort study | Not applicable | Clinical diagnosis of BCNS | Progression-free survival and response rate | 24–19 | Median progression-free survival: 19.1 months (95% CI 74.0–99.6) | Probability of PR within 3 months: 93.3% (95% CI 79.9–99.6) |
| Sohn et al.     | Itraconazole 0.7% gel twice daily | Phase-2 open-label intrapatient | 3b                  | Patients with >3 BCCs annually | Change in BCC tumour area | LDE225: 0.25%: 3 | Total BCCs treated: 65 | Itraconazole: 9 Vehicle: 9 | Change at week 4: 0.04% | Change at week 12: 8.9% |
| Epstein et al.  | 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 | Vismodegib 2%: 6 | Total number of BCCs at baseline: 21 | Patidegib 4%: 6 Vehicle: 5 | Change at week 4: 0.03% | Mean number of BCCs at week 26: 7 |
| Skvara et al.   | Sonidegib 0.25% and 0.75% cream twice daily | Phase-2 double-blind, parallel assignment^ | 1b                  | Clinical diagnosis of BCNS with BCCs on 2 different body parts | Percentage of BCCs with clearance | LDE225 0.75%: 8 LDE225 0.25%: 3 LDE225 0.75%: 7 | Total number of BCCs at baseline: 14 | Part 1–4 weeks Vehicle: 8 | Decrease in SEB tumour size at week 4: 7.0 | Mean change in SEB tumour size at week 4: 7.0 |

*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.
### 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 22 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, 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                                                                                                           |
| 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                                               |
| Hoffmann et al. 2021 (19)                  | HF-BCC patient with >100 BCCs and sonidegib 200 mg once every day BCNS patient on and off treatment for >3 years (reintroduction after recurrence and discontinuation after complete response) | Clinical remission of all but 1 BCC after 9 months                                                                                     |
| Mendes et al. (18)                         |                                                                                   | *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.

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

| Hedgehog pathway inhibitor | Tang et al. (11, 12) | Lear et al. (14) | Dreno et al. (15) Group A* | Dreno et al. (15) Group B* |
|----------------------------|----------------------|------------------|-----------------------------|----------------------------|
| Dosage                     | Vismodegib 150 mg daily | Sonidegib 400 mg daily | Vismodegib 150 mg daily alternated with placebo | Vismodegib 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             | 38% (3) | 73% (83) | 63% (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/asthma         | 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 |
| Withdraw consent           | NM | NM | 10% (12) | 12% (13) |
| Investigators decision     | NM | NM | 2% (2) | 5% (6) |
| Disease progression        | NM | NM | 3% (3) | 3% (3) |
| Died                       | NM | 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.

### Topical hedgehog pathway inhibitor

Three randomized-vehicle-controlled phase-2 trials investigating twice daily application of topical HPIs were registered at clinicaltrials.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...
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 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

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

| Side-effects | Skvara et al. (24) | Epstein et al. (23) | Sohn et al. (37) |
|--------------|-------------------|-------------------|-----------------|
|              | Part I            | Part II           | Part II         | Patidegib 2% n = 6 | Patidegib 4% n = 6 | Vehicle n = 5 | Itraconazole 0.7% & vehicle* n = 9 |
|              | LDE225 0.75% & vehicle n = 8 | LDE225 0.25% n = 3 | LDE225 0.75% n = 7 | 0 (0%) | 0 (0%) | 1 (20%) | Pneumonia 0 (0%) |
| 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.
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

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) | – 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. |
| Banvolgyi et al. (27) | Retrospective cohort – 5 | 4 | Unknown | Not described | |
| Van Eek et al. (28) | Case report – 5 | 1 | 19 | Not described | – In 3 cases, at least 19 BCCs developed within 2 years after discontinuing vismodegib of unknown treatment duration. |
| 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 – 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 |
| Soura et al. (31) | Case report – 5 | 1 – BCNS | 79 | Not described | |
| Piccirillo 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 Eek 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 off-on 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.
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 tretinoin 0.7% gel application for 4 weeks appeared not to be effective in 9 patients and topical patitidegib 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 patitidegib 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: BJA, 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.

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