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ORIGINAL RESEARCH

Benefit–risk assessment of sonidegib and vismodegib in the treatment of locally advanced basal cell carcinoma

Antonio J García Ruiz[1], Nuria García-Agua Soler[1], Enrique Herrera Acosta[2], Iris Zalaudek[3], Josep Malvehy[4,5]

[1]Pharmacology Department, University of Málaga, Institute of Biomedical Research in Malaga (IBIMA), Malaga, Spain; [2]Dermatology Department, Hospital Virgen de la Victoria, Malaga, Spain; [3]Dermatology Department, University of Trieste, Trieste, Italy; [4]Dermatology Department, Hospital Clinic of Barcelona, Institut d'Investigacions Biomediques August Pi I Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; [5]Centro de Investigacion Biomedica en Red (CIBER) on Rare Disease, Instituto de Salud Carlos III, Madrid, Spain

Abstract

Background: Sonidegib and vismodegib are Hedgehog pathway inhibitors (HhIs) that play a relevant role in the management of locally advanced basal cell carcinoma (laBCC). This study compared the efficacy and safety of both HhIs based on their available data using effect size measures such as number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

Methods: We reviewed data from pivotal trials of sonidegib (BOLT) and vismodegib (ERIVANCE). The NNT for sonidegib and vismodegib was calculated from objective response rate (ORR) values. The NNH was calculated from data relating to treatment discontinuation due to adverse events (AEs) and incidence of AEs. The LHH was calculated as the ratio between the corresponding NNH and NNT.

Results: For sonidegib (200 mg), the NNT for ORR at 18 months was 1.65 (95% CI 1.35–2.01) whilst that for vismodegib (150 mg) at 21 months was 2.10 (95% CI 1.65–2.82). The NNH related to treatment discontinuation due to AEs was 1.9 (95% CI 1.6–2.5) for sonidegib and 1.8 (95% CI 1.4–2.2) for vismodegib. The LHH for sonidegib and vismodegib related to treatment discontinuation due to AEs was 1.14 and 0.84, respectively, whilst the LHH according to AEs of grade ≥3 was 1.41 for sonidegib and 0.85 for vismodegib.

Conclusions: Sonidegib showed a better benefit–risk ratio compared to vismodegib, being more likely to achieve therapeutic response than to AEs leading to discontinuation. These results should be confirmed in clinical practice and/or in a direct comparison study.

Keywords: locally advanced basal cell carcinoma, sonidegib, vismodegib.

Citation

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Introduction

Basal cell carcinoma (BCC) is a skin carcinoma derived from epidermal cells mostly located on sun-exposed sites with the potential to progress to locally advanced (laBCC) or metastatic BCC.[1] Specifically, laBCC is defined as BCC with invasion of the surrounding structures where surgery and radiotherapy are often not viable treatment options.[2] BCC is the most common malignant tumour in white individuals with the highest incidence in Australia, followed by the United States and Europe. The average incidence rate reported in European countries was 76.21/100,000 person-years.[3] laBCC accounted for 0.8% of all BCC cases in a retrospective cohort study in the United States, with an incidence of 2/10,000 persons with higher rates for patients older than 65 and men.[3]

The treatment of laBCC is difficult, and a multidisciplinary tumour board should decide the appropriate management by considering the benefits of surgical or pharmacological interventions.[1] Some cases of laBCC may be surgically removed; however, the challenge remains to determine whether laBCC is fully resectable. For those patients for whom surgery is contraindicated or who have perineural involvement, radiotherapy is a treatment option. In case of positive margins following surgery, radiotherapy can be used as adjuvant therapy. However, radiotherapy is not recommended for patients with tumours that recur after prior radiotherapy or

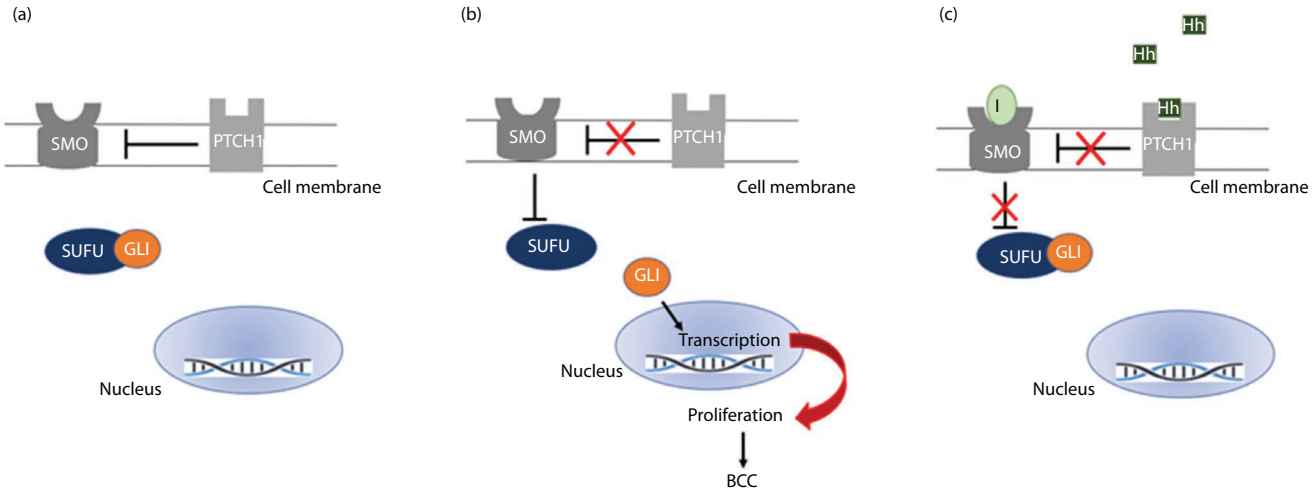
for those with genetic conditions that predispose them to skin cancers.[4] Due to the concerns with long-term sequelae associated with radiotherapy, it is also discouraged in patients younger than 60 years old. Therefore, in some cases, patients reach a point in their treatment journey where standard options, such as surgery and radiotherapy, are no longer viable and alternative treatment approaches, such as the use of the Hedgehog (Hh) pathway inhibitors (HhIs), should be considered.

The Hh intracellular signalling pathway is essential for the regulation of cell growth and differentiation during embryonic development; however, in adult tissues under normal conditions, it is silent. An aberrant activation of this pathway is the trigger for the pathogenesis of BCC.[5] A family of secreted ligands activates this pathway by interacting with the transmembrane receptor Patched (PTCH) and blocking inhibition on Smoothened (SMO)[6] (Figure 1a). Mutations of the receptor PTCH1 are the most frequent genetic alterations found in BCC. They prevent the inhibition of PTCH on SMO, allowing the activation of downstream signals, even in the absence of ligands, and lead to uncontrolled cell growth.[7] Vismodegib and sonidegib, HhIs with affinity for SMO, deactivate the Hh signalling pathway and subsequently block signal transduction (Figure 1b). These two HhIs are indicated for the treatment of laBCC in cases where surgery and radiotherapy are inappropriate.[8,9] The efficacy and safety of sonidegib and vismodegib were evaluated in the pivotal trials BOLT and ERIVANCE, respectively, whose main features are summarized in Table 1.[10]

Although vismodegib and sonidegib play a relevant role in the management of patients with laBCC, their clinical differences are unknown due to the absence of controlled randomized trials or direct comparison of the two inhibitors. However, some previous publications attempted to indirectly address this point.

In a matching-adjusted indirect comparison, the main difference between both study populations was the greater number of patients with previous surgery and radiotherapy in ERIVANCE.[11] By using the propensity score matching technique, a better efficacy of sonidegib was observed compared to vismodegib (Table 2). However, the study presented limitations such as not having relative effect examinations and the mean outcome being measured at different times.[11] In addition, a group of experts in the management of laBCC discussed the clinical differences between sonidegib and vismodegib by comparing the designs of their pivotal studies and the subsequent efficacy and safety results.[10] Although vismodegib was evaluated with the Response Evaluation Criteria In Solid Tumours (RECIST) and sonidegib with the stringent modified RECIST criteria (mRECIST), the inclusion of a preplanned analysis to adjust the outcomes with RECIST criteria in BOLT allowed the experts to discuss centrally reviewed relative efficacy outcomes for the two treatments (Table 3).[10,12] In terms of tolerability, sonidegib showed approximately 10% lower incidence of most adverse events (AEs) compared to vismodegib at final analyses, and the reported treatment-emergent AEs were slightly less frequent and severe. The authors stated that, in theory, the potential differences in efficacy and toxicity

Figure 1. Altered Hh signalling pathway and mechanism of action of vismodegib and sonidegib. Reproduced from ref.[36] following the license terms of CC BY 4.0.



(a) In absence of ligands, the receptor Patched (PTCH1) inhibits Smoothened (SMO), allowing the protein suppressor of fused (SUFU; pathway regulator) to bind and inhibit the transcription factors GLI. **(b)** Altered Hedgehog (Hh) signalling pathway in basal cell carcinoma (BCC): a genetic alteration found in BCC of the receptor PTCH1, which prevents inhibition on SMO and allows the activation of downstream signals even in the absence of Hh ligands, leading to uncontrolled cell growth. **(c)** Mechanism of action of the inhibitors, vismodegib and sonidegib, which present affinity for SMO, blocking the Hh signalling pathway and consequently signal transduction.

Table 1. Similarities and differences of the pivotal clinical trials of vismodegib and sonidegib.[30–32,37,38]

	BOLT	ERIVANCE
Study design	Phase II	Phase II
Treatment	Randomized 1:2 to sonidegib 200 mg QD (laBCC, *n*=66) or 800 mg QD (laBCC, *n*=128)	Vismodegib 150 mg QD (laBCC, *n*=63)
Inclusion criteria	≥18 years old Inoperable laBCC or surgery is contraindicated, and radiotherapy is contraindicated or inappropriate Adequate bone marrow, liver and renal function	≥18 years old Inoperable laBCC and prior radiotherapy, unless radiotherapy is contraindicated or inappropriate
BCC assessment criteria	mRECIST* and RECIST	RECIST
Primary endpoint	ORR (CR+PR) by central review	ORR (CR+PR) by central review
Secondary endpoints	ORR by investigator review DOR PFS OS Time to response Safety QoL	ORR by investigator review DOR PFS OS Safety QoL
Follow-up		
Central review	6 months 12 months 18 months 30 months 42 months	9 months 21 months
Investigator review	6 months 12 months 18 months 30 months 42 months	9 months 21 months 39 months

*mRECIST is a more stringent composite multimodal algorithm compared to RECIST, which determines responses based on the outcomes of three instruments combined (MRI, colour photography and histology). Response according to MRI criteria: >30% reduction in the sum of longest diameters of target lesions; response determined in standard and annotated bidimensional colour photography from the WHO guidelines: >50% reduction in the sum of products of perpendicular diameters of target lesions; response based on histology in multiple biopsy specimens surveying the lesion area: a minimum of two negative biopsies.
CR, complete response; DOR, duration of response; laBCC, locally advanced basal cell carcinoma; mRECIST; modified RECIST; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QD, once daily; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

between sonidegib and vismodegib may be explained by the more extensive distribution of sonidegib in the skin compared with vismodegib.[10] Moreover, unlike vismodegib, sonidegib allows the option of an every other day dose before treatment suspension in case that intolerable AEs appear.[13] However, they recognized the difficulty of obtaining conclusions and directed this analysis to the contextualization of the results.[10]

Despite the effort to establish the clinical differences between sonidegib and vismodegib, none of these studies led to a significant conclusion that favours the use of one HhI over the other. In addition, patients with laBCC are especially vulnerable due to their clinical situation, coping with tumour growth, itching, bleeding, ulcerations and aesthetic problems, that cause stress or depression and impair their quality of life.[14,15]

Table 2. Matching-adjusted indirect comparison of efficacy in patients with laBCC from the studies BOLT and ERIVANCE.[11]

Patients with laBCC	Sonidegib 200 mg		Vismodegib 150 mg
	Prematched	Postmatched	
Follow-up (months)	18	18	21
ORR, *n* (%)	37 (56.1%) (95% CI 44.1–68.0)	(56.7%) (95% CI 44.7–68.6)	30 (47.6%) (95% CI 35.5–60.6)
Sensitivity analysis (similar criteria to ERIVANCE)			
ORR, % (95% CI)	60.6% (48.4–72.4)	59.5% (47.6–71.3%)	

laBCC, locally advanced basal cell carcinoma; ORR, objective response rate.

Table 3. Efficacy in patients with laBCC in BOLT and ERIVANCE studies.[30,32]

laBCC	Sonidegib 200 mg	Vismodegib 150 mg
Assessment criteria	RECIST	RECIST
Months follow-up	18	21
ORR, *n* (%)	40 (60.6%) (95% CI 47.8–72.4)	30 (47.6%) (95% CI 35.5–60.6)
CR, *n* (%)	14 (21.2%)	14 (22.2%)
PR, *n* (%)	26 (39.4%)	16 (25.4%)
SD, *n* (%)	20 (30.3%)	22 (34.9%)
PD, *n* %	1 (1.5%)	8 (12.7%)
Unknown, *n* (%)	5 (7.6%)	3 (4.8%)

CR, complete response; laBCC, locally advanced basal cell carcinoma; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

HhIs have a mild but sometimes disabling profile of tolerability. Hence, in order to guarantee treatment compliance, physicians and patients should understand and discuss the benefits and the risks of each of the treatment options.

Under these circumstances, we considered that a comparative assessment of the benefit–risk profile based on available data of both sonidegib and vismodegib, relating to evidence-based tools, such as the number needed to treat (NNT), the number needed to harm (NNH), and the likelihood to be helped or harmed (LHH), may provide valuable information in the treatment of patients with laBCC. NNT is a measure of the efficacy of a treatment based on a calculation of the number of patients who will likely need to be treated with the studied treatment to benefit a single patient relative to the control group,[16,17] whereas NNH is its counterpart and indicates the number of patients who need to be treated before one more patient will experience harm compared to a control group.[16,17] LHH is a simple tool to assess the benefit–risk ratio, calculated from NNT and NNH.[17] They are simple and intuitive methods that have been widely used in clinical literature assessing the benefit–risk ratio of different treatments.[18] For example, a recent NNT analysis showed a prominent mortality benefit with vertebral augmentation over non-surgical management after vertebral compression fractures.[19] NNT measure has also been used to determine the most effective treatments in multiple sclerosis, stroke thrombectomy and atrial fibrillation.[20–23] In addition, it is recommended to include NNT in randomized controlled trials to quantify the magnitude of the treatment effect[24] by offering an additional advantage compared to other binary outcomes and presenting a relatively straightforward clinical interpretation of clinical trials with relevance to daily practice.[16] These effect size measures are valuable tools in assisting clinicians in the decision between alternative therapeutic interventions.[17] Other healthcare stakeholders, including regulatory authorities, healthcare decision-makers and pharmaceutical companies, use these metrics as a supportive tool in benefit–risk assessment when sustained by thorough evidence synthesis.[18,25–27]

Therefore, the objective of this study was to determine the NNT, the NNH in relation to treatment interruption due to AEs or physician decision, incidence of AE grade ≥3 and serious AEs related to the treatment, and the corresponding LHH of sonidegib and vismodegib from the efficacy and safety results of their corresponding pivotal studies (BOLT *versus* ERIVANCE).

Methods

Study population and time points

This analysis reviewed data of patients with laBCC not amenable to curative surgery or radiation therapy that participated in the pivotal trials of sonidegib (BOLT) and vismodegib (ERIVANCE). Vismodegib was also assessed in two other phase II studies, STEVIE[28] and MIKIE.[29] However, because

of important differences, an expert group considered the data from these studies to be inappropriate for direct comparison of efficacy and their review therefore focused on ERIVANCE and BOLT pivotal studies.[10] No real-world evidence studies were available at the time of this analysis.

The time points selected for the efficacy analysis correspond to the closest follow-up time points across the pivotal trials based on central review: 18 months for sonidegib[30] and 21 months for vismodegib.[31] These time points were considered by an expert panel as the most representative ones for comparison of both inhibitors.[10] An additional analysis based on the long-term results was also conducted using the efficacy outcomes, reviewed by investigator, obtained after 42 months with sonidegib[12] and 39 months with vismodegib.[32] The outcomes for the safety analysis were considered from the long-term follow-up periods: 42 months for sonidegib[33] and 39 months for vismodegib.[32]

NNT analysis

The NNT usually corresponds to the inverse of an absolute risk reduction and is computed as the difference between event rates in two groups (the difference between the expected event rate and control event rate) (Table 4).[16] In this analysis, the NNT for sonidegib and vismodegib were calculated using the objective response rate (ORR), the primary endpoint of BOLT and ERIVANCE trials. ORR was defined as the proportion of patients with a best overall response of complete response or partial response. The NNT analysis for sonidegib was conducted using the ORR values determined by central review using RECIST criteria (Table 3).[10,12] For the NNT analysis from the long-term efficacy outcomes, ORR according to investigator review was used, as it was the only efficacy outcome existing from vismodegib in the long-term follow-up.[12,32] It should be noted that duration of response was not considered in the analysis; however, sonidegib and vismodegib showed a mean duration of response of 26.1 and 26.2 months, respectively, in the long-term analysis.[12,32]

As the pivotal studies of sonidegib and vismodegib did not have a control group, baseline data were used instead; hence, the number of patients who achieve a favourable effect at the start of the study was 0/*N* (patients with favourable effect/total of study population).

NNH analysis

The NNH is calculated based on the absolute risk increase, which is the difference between the event rate of the adverse event in the experimental group and in the control group (Table 4). In this analysis, the NNH for both sonidegib and vismodegib was calculated following three different parameters considered the most relevant for the maintenance of the patient quality of life and treatment compliance: treatment discontinuation due to AEs, physician or patient decision, incidence of AEs of grade ≥3, and serious AEs related to the treatment. AEs from both pivotal trials were reviewed according to the Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) classification.[34]

Table 4. Expressions for the measures of NNT, NNH and LHH.

Measure	Expression
NNT	NNT = 1/ARR = 1/(EER – CER)
NNH	NNH = 1/ARI = 1/(AER – CER)
LHH	(1/NNT)/(1/NNH)

AER, adverse event rate in experimental group; ARI, absolute risk increase; ARR, absolute risk reduction; CER, (adverse) event rate in control group; EER, expected event rate in experimental group; LHH, likelihood to be helped or harmed; NNH, number needed to harm; NNT, number needed to treat.

LHH analysis

The LHH is the ratio of the absolute risk reduction for prevention of an adverse outcome (1/NNT) *versus* an absolute risk increase for safety (1/NNH) (Table 4).

Odds ratio

The odds ratio (OR) in terms of benefit and risk between sonidegib and vismodegib was also calculated using 2×2 tables.

Results

Data from a total of 129 patients with laBCC, 66 receiving 200 mg/day of sonidegib (BOLT trial) and 63 receiving 150 mg of vismodegib (ERIVANCE trial), were included in the analysis. As previously mentioned, the patient baseline characteristics of both studies were similar, with the main difference being the greater number of patients with previous surgery and radiotherapy in ERIVANCE.[10]

NNT of sonidegib and vismodegib

For sonidegib (200 mg), the NNT for ORR at 18 months was 1.65 (95% CI 1.35–2.01); thus, treating less than two patients with sonidegib resulted in a patient with an objective response. For vismodegib (150 mg), the NNT at 21 months was 2.10 (95% CI 1.65–2.82), indicating that two patients need to be treated with vismodegib before one patient had an objective response (Table 5).

The OR for patients obtaining an objective response was 1.54 (40/26) for sonidegib and 0.91 (30/33) for vismodegib. The OR of sonidegib *versus* vismodegib was 1.54/0.91 = 1.69, indicating a superior efficacy of 69% for sonidegib over vismodegib.

Table 5. NNT analysis of sonidegib and vismodegib based on the primary endpoint of the corresponding pivotal trials (BOLT *versus* ERIVANCE).

Drug (dose)	Time (months)	*n*	Patients with ORR	NNT (95% CI)
Sonidegib (200 mg/day)	18	66	40[a]	1.65 (1.35–2.01)
Vismodegib (150 mg/day)	21	63	30	2.10 (1.65–2.82)

[a]ORR from clinical trial BOLT after adjusting using RECIST criteria. Efficacy data from refs.[10,12,31]
NNT, number needed to treat; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours.

Table 6. NNH analysis of sonidegib and vismodegib based on treatment discontinuation and incidence of severe AE notified in the corresponding pivotal trials (BOLT *versus* ERIVANCE).

Drug (dose)	ARI	NNH (95% CI)	*p* value χ^2 test
Patients abandoning treatment due to AEs, patient decision and physician decision			
Sonidegib (200 mg)	51.5%	1.9 (1.6–2.5)	0.5155
Vismodegib (150 mg)	57.0%	1.8 (1.4–2.2)	
Patients with grade ≥3 AEs			
Sonidegib (200 mg)	42.13%	2.4 (1.8–3.6)	0.0607
Vismodegib (150 mg)	55.8%	1.8 (1.5–2.3)	
Patients with serious AEs related to treatment			
Sonidegib (200 mg)	5%	19.75 (20 to infinite)	0.2512
Vismodegib (150 mg)	9%	11.56 (6.8–30.6)	

AE, adverse event; ARI, absolute risk increment; NNH, number needed to harm.
Safety data from refs.[10,30–33]

NNH of sonidegib and vismodegib

Table 6 shows the NNH for sonidegib (200 mg/day) and vismodegib (150 mg/day) corresponding to three different safety outcomes: treatment discontinuation due to AEs, patient or physician decision, incidence of AEs of grade ≥3, and serious AEs related to treatment.

The OR for treatment discontinuation due to AEs of sonidegib was 1.135 (42/37), whilst that of vismodegib was 1.311 (59/45), indicating that a patient is more likely to discontinue treatment due to AEs with vismodegib than with sonidegib. The OR between sonidegib and vismodegib indicated a 15% higher risk of treatment discontinuation due to AEs with vismodegib than with sonidegib (OR = 1.311/1.135 = 1.155).

LHH of sonidegib and vismodegib

The LHH values for sonidegib (200 mg/day) and vismodegib (150 mg/day) are shown in Table 7. All LHH for sonidegib were >1, which can be interpreted as sonidegib being more likely to help than to harm a patient. However, the LHH for vismodegib considering treatment discontinuation and incidence of grade ≥3 AEs was <1, indicating that the likelihood of achieving an objective response was less than the likelihood of treatment discontinuation or incidence of grade ≥3 AEs. In the case of LHH corresponding with serious AEs, both drugs are more likely to achieve objective response than serious AEs, with the likelihood being double for sonidegib compared to vismodegib.

Long-term NNT, NNH and LHH of sonidegib and vismodegib

The NNT, NNH and LHH results of sonidegib and vismodegib at 42 months and 39 months, respectively, are shown in Table 8. These results were aligned with the first analysis, obtaining an OR for the benefit–risk ratio in favour of sonidegib *versus* vismodegib of 1.35, indicating the superiority of sonidegib in long-term efficacy and safety of compared to vismodegib.

Discussion

This analysis used data from the pivotal clinical trials BOLT and ERIVANCE to compare the two Hhl therapies – sonidegib and vismodegib – in the treatment of patients with laBCC not amenable to curative surgery or radiation therapy, by calculating the NNT values for achieving objective response to

treatment, NNH values for treatment discontinuation due to AEs, patient or physician decision as well as due to severe AEs, and the corresponding LHH values. The outcomes reported in both trials were translated into these effect size measures to ease the comparison between both treatments and facilitate informed decision-making in clinical practice.

Both HhIs proved beneficial in the treatment of laBCC; however, based on our analysis, sonidegib appeared to be a 69% more effective than vismodegib, it being necessary to treat less than two patients (NNT 1.65) with sonidegib to achieve an objective response compared to more than two patients for vismodegib (NNT 2.10). Additionally, the analysis of NNH of sonidegib and vismodegib and the corresponding OR indicated that the risk of treatment discontinuation due to AEs was slightly higher for vismodegib than for sonidegib. Furthermore, the risks of grade ≥3 AEs and serious AEs related to treatment were higher for vismodegib than for sonidegib. The LHH of sonidegib indicated that sonidegib was more likely to result in a therapeutic response than to harm the patient (LHH 1.14) whilst the use of vismodegib was more likely to result in treatment discontinuation due to AEs (LHH 0.84) or grade ≥3 AEs (LHH 0.85) than to achieve objective response. Nonetheless, in the long-term, both drugs presented a positive benefit–risk profile, more in favour of sonidegib, being 35% superior in terms of LHH compared to vismodegib.

Despite the similarities between sonidegib and vismodegib in their mechanism of action and indication, they have not yet been compared in a randomized controlled trial. Herein, we have established evidence-based recommendations to choose between them with better criteria by clinicians.

Another significant difference between sonidegib and vismodegib is their pharmacokinetic profile. Sonidegib is characterized by an extensive distribution in tissues due to its high volume of distribution (>9000 L) compared to vismodegib, which has limited tissue penetration being largely confined to the plasma (volume of distribution of 16–27 L).[8,9] As a result, the concentration of sonidegib is six times greater in the skin than in plasma. The clear lipophilic character of sonidegib that suggests its more extensive distribution in the skin compared to vismodegib may account for their possible differences in efficacy and toxicity.[9] Other differences in the pharmacokinetic profiles between sonidegib and vismodegib include a longer half-life and a non-concentration-dependent plasma protein binding for sonidegib.[8,9] Unlike vismodegib, the pharmacokinetic properties of sonidegib are dose proportional, allowing the correlation of dose with efficacy and dose-dependent AEs.[35] Therefore, temporary dose interruption (a maximum of 3 weeks) or dose reduction (200 mg every other day) of sonidegib therapy may be possible for the management of AEs such as creatine phosphokinase elevations or muscle-related AEs.[13] Even though these pharmacokinetic differences are known, studies that correlate them with the efficacy and

Table 7. LHH analyses of sonidegib and vismodegib.

Parameters considered for LHH	Sonidegib (200 mg)	Vismodegib (150 mg)
ORR/patients abandoning treatment due to AEs, patient decision or physician decision	1.14	0.84
ORR/patients with grade ≥3 AEs	1.41	0.85
ORR/patients with serious AEs related to treatment	11.96	5.55

AE, adverse event; LHH, likelihood to be helped or harmed; ORR, objective response rate.

Table 8. NNT, NNH and LHH analysis of sonidegib and vismodegib based on the long-term results of the corresponding pivotal trials (BOLT *versus* ERIVANCE).

Drug (dose)	Time (months)	Patients with objective response[a] (*n*/*N*)	NNT	Patients discontinued[b] (*n*/*N*)	NNH	LHH	OR
Sonidegib (200 mg/day)	42	49/66	1.34	42/79	1.88	1.40	1.32
Vismodegib (150 mg/day)	39	38/63	1.66	59/104	1.76	1.06	

[a]Objective response according to investigator review as it was the only efficacy outcome for vismodegib in the long-term follow-up.
[b]Treatment discontinuation due to TEAE, physician decision or patient decision.
LHH, likelihood to be helped or harmed; NNH, number needed to harm; NNT, number needed to treat; ORR, objective response rate; TEAE, treatment emergent adverse event.
Efficacy data from ref.[12] (sonidegib) and ref.[32] (vismodegib).

safety of sonidegib and vismodegib are needed. Additional real-world data of clinical practice use of both HhIs will be helpful to identify the real differences and the patients that may benefit most from these therapies.

Despite the results in real practice being unknown, the better benefit–risk ratio of sonidegib shown in this analysis may help physicians decide on the best treatment option for their patients. In case of AEs with vismodegib, sonidegib and its flexible dose schedule can be an alternative. In patients with genodermatosis, such as Gorlin syndrome, in which a long-term treatment schedule must be assumed, a lower toxicity has a positive impact on patient quality of life. In these cases, the LHH analysis is even more relevant.

Limitations

The results of this analysis should be considered with precaution because the pivotal trials of sonidegib and vismodegib were single-arm studies that did not have a comparative control group. Another limitation of the current analysis that needs to be acknowledged is the difference in treatment exposure time. Further studies in real clinical practice may confirm this assessment.

Conclusions

In view of the lack of direct comparative studies between sonidegib and vismodegib and of significant results from the currently available indirect comparisons, the efficacy and safety of both drugs were comparatively assessed using the available data from the corresponding pivotal clinical trials BOLT and ERIVANCE. This comparison was performed using effect size measures: NNT, NNH and LHH. This analysis showed that sonidegib has a better benefit–risk ratio compared to vismodegib and is more likely to achieve therapeutic response than it is to cause AEs leading to discontinuation. These results may assist patients, physicians and healthcare decision-makers in choosing the optimal treatment for laBCC.

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Correspondence: Antonio J García Ruiz, Pharmacology department, University of Málaga. Institute of Biomedical Research in Malaga (IBIMA), Malaga, Spain. Email: ajgr@uma.es

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