Review

A review of the safety, efficacy, and administration of hedgehog inhibitors for the treatment of advanced basal cell carcinoma: an expert consensus panel

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Abstract

Hedgehog inhibitors are approved for the treatment of locally advanced basal cell carcinomas in patients who are not surgical candidates or have had recurrence following surgical treatment. This expert consensus panel further characterizes the efficacy and safety of hedgehog inhibitors while providing clinical guidance on their dosing, laboratory monitoring, and supplementation. A literature review was completed on November 1, 2024, using the keywords “basal cell carcinoma,” “hedgehog inhibitor,” “sonidegib,” and “vismodegib.” An expert panel of 9 dermatologists reviewed and assigned levels of evidence to the relevant articles and created consensus statements regarding hedgehog inhibitors, with correlating strength of recommendations, using the modified Delphi process. Of the 304 articles identified, 23 met the selection criteria and were reviewed. The panel unanimously adopted 9 consensus statements and recommendations; three were given a strength of recommendation of “A,” two were given a “B,” and four were given a “C.” Sonidegib and vismodegib have similar efficacy in treating advanced basal cell carcinomas, but sonidegib has lower rates and a greater delay in onset of adverse events. Sonidegib has a significantly greater volume of distribution and half-life than those of vismodegib. Dosing interruptions have not been shown to reduce the efficacy of hedgehog inhibitors, and L-carnitine supplementation can help reduce muscle spasms.

Introduction

Basal cell carcinoma (BCC), a type of nonmelanoma skin cancer, is the most common cutaneous malignancy and cancer overall in the world.[1] BCCs are associated with substantial morbidity worldwide and can cause significant local tissue destruction and disfigurement.[1] While they rarely metastasize, very aggressive forms of BCC can spread to visceral organs and have high mortality rates.[2] As the rates of BCCs continue to rise, they pose an increasingly important risk to global health. BCCs are generally treated with procedural interventions including local excision, electrodessication and curettage, or Mohs micrographic surgery.[3] However, certain BCCs are very large and infiltrate deep into the tissue, termed locally advanced basal cell carcinoma (laBCC), and frequently result in suboptimal outcomes when treated surgically given the degree of tissue destruction caused by cancer and/or surgical repair.[4]

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Hedgehog inhibitors (HHIs), a class of oral medications preventing the development of BCC by suppressing the overactivity of the hedgehog pathway, are approved by the Food and Drug Administration (FDA) for the treatment of laBCC in patients for whom surgery or radiation therapy are not recommended.[5] Sonidegib and vismodegib are the HHIs currently approved by the FDA for the treatment of laBCC following the success of their pivotal trials in 2015 and 2012, respectively.[6] HHIs provide an effective, alternative therapeutic option for patients with difficult-to-treat BCC, but their use is limited due to concerns with higher rates of adverse events, unclear laboratory monitoring requirements, and clinician familiarity. Thus, this expert consensus panel aims to provide recommendations on the overall safety, efficacy, and proper administration of HHIs, including target patient populations, laboratory monitoring, and dosing regimens.

Methods

Literature Search and Study Selection

A comprehensive literature search of PubMed, Scopus, and Google Scholar was completed on November 1, 2024, using the keywords "basal cell carcinoma," "hedgehog inhibitor," "sonidegib," and "vismodegib" along with the Boolean term "AND" for English-language original research articles, systematic reviews, and meta-analyses without date restrictions. Articles were screened for relevance to the safety, efficacy, and practical application of HHIs for the treatment of advanced BCC. A panel of nine dermatologists with expertise in managing BCC was assembled. Articles that met the inclusion criteria were distributed to the panelists for review and assigned a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[7] The three levels include level 1 (high quality patient-oriented evidence), level 2 (lower quality patient-oriented evidence), and level 3 (consensus guidelines, usual practice, opinion, or disease-oriented evidence).[7] No International Review Board approval was required for this study.

Development of Consensus Statements

The panel convened on November 18, 2024, to review and discuss the selected literature and craft consensus statements that addressed the efficacy, safety profile, and recommended usage of HHIs for the treatment of laBCC. A modified Delphi method was used to achieve a consensus for each statement.[8] This process requires supermajority approval for the adoption of each recommendation, potentially after multiple rounds of real-time voting. The Delphi technique is a widely adopted and accepted method for creating expert recommendations in dermatology.[9-12] Consensus statements were also assigned either a strength of recommendation of A (recommendations with consistent, high-quality patient-oriented evidence), B (recommendations with inconsistent and/or lower quality patient-oriented evidence), or C (recommendations based on expert consensus, opinion, case studies, etc). Of note, a strength of recommendation of C is not inherently weaker than A, but rather objectively reflects the type of evidence supporting a recommendation.

Results

Literature Search and Study Selection

The initial literature search resulted in 304 articles. Following a thorough screening, 23 articles relevant to the research questions were selected and distributed to the panelists for review prior to the roundtable discussion.

Levels of Evidence Designation

Of the 23 articles, the panel assigned level 1 evidence to 9 articles,[13-21] level 2 evidence to 9 articles,[22-30] and level 3 evidence to 5 articles[31-35] (Table 1).

Consensus Statements

The panel crafted nine consensus statements regarding the efficacy, safety, target patient populations, pharmacodynamics, and dosing schedules of HHIs. The 9 consensus statements were all unanimously (9/9) accepted. Three consensus statements were assigned a strength of recommendation of A, two were assigned a strength of recommendation B, and four were assigned a strength of recommendation C (Table 2).

Statement 1: *HHIs are an effective treatment that can help reduce the tumor burden of locally advanced basal cell carcinomas as a primary or neoadjuvant therapy prior to Mohs or other interventions. (SORT Level A)*

There is substantial evidence supporting the efficacy of HHIs in the treatment of advanced BCC for both sonidegib and vismodegib. In the ERIVANCE phase II trial, patients with laBCC taking 150mg of vismodegib daily achieved an objective response rate (ORR) of 43% with a 7.6-month median duration of response.[36] In the 21-month follow up to the ERIVANCE study, the ORR for laBCC increased to 47.6% (complete response in 22.2% and partial response in 25.4%), and the median duration of response was 9.5 months per central review.[21] Final analysis at 39 months was only investigator assessed with an ORR of 60.3% in the laBCC group and 48.5% in the metastatic BCC group.[37] Additionally, in the international, open-label STEVIE trial, investigator assessed response rates for patients on vismodegib were 68.5% for laBCC and 36.9% for metastatic BCC.[28]

In 2015, sonidegib was approved following the randomized, double-blind phase II BOLT trial showing a 43% ORR for patients with laBCC in the 200mg group, using the more stringent modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[20] In the 12-month follow-up analysis of the BOLT trial, the ORRs for the 200mg sonidegib group were 57.6% per central review and 71.2% per investigator review for laBCC, and among responsive patients, more than 50% had responses last-

Table 1. *SORT Criteria Level of Evidence for Articles Pertaining to the Treatment of Locally Advanced Basal Cell Carcinoma With Hedgehog Inhibitors.*

Article	Level of Evidence
Cannon JGD, Tran DC, Li S, Chang AS. Levocarnitine for vismodegib-associated muscle spasms: a pilot randomized, double-blind, placebo-controlled, investigator-initiated trial. *J Eur Acad Dermatol Venereol*. 2018;32(7):e298-e299. doi:10.1111/jdv.14844	1
Cantisani C, Musolff N, Longo C, et al. Dynamic optical coherence tomography evaluation in locally advanced basal cell carcinoma during sonidegib treatment. *J Eur Acad Dermatol Venereol*. 2024;38(5):967-973. doi:10.1111/jdv.19806	2
Dinehart MS, McMurray S, Dinehart SM, Lebwohl M. L-Carnitine Reduces Muscle Cramps in Patients Taking Vismodegib. *SKIN*. 2018;2(2):90-95.	3
Dréno B, Kunstfeld R, Hauschild A, 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(3):404-412. doi:10.1016/S1470-2045(17)30072-4	1
Dummer R, Guminski A, Gutzmer R, et al. The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma. *J Am Acad Dermatol*. 2016;75(1):113-125.e5. doi:10.1016/j.jaad.2016.02.1226	1
Dummer R, Guminksi A, Gutzmer R, et al. Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study. *Br J Dermatol*. 2020;182(6):1369-1378. doi:10.1111/bjd.18552	1
Dummer R, Lear JT, Guminski A, Leow LJ, Squittieri N, Migden M. Efficacy of sonidegib in histologic subtypes of advanced basal cell carcinoma: Results from the final analysis of the randomized phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) trial at 42 months. *J Am Acad Dermatol*. 2021;84(4):1162-1164. doi:10.1016/j.jaad.2020.08.042	1
Gutzmer R, Loquai C, Robert C, et al. Key Clinical Adverse Events in Patients with Advanced Basal Cell Carcinoma Treated with Sonidegib or Vismodegib: A Post Hoc Analysis. *Dermatol Ther (Heidelb)*. 2021;11(5):1839-1849. doi:10.1007/s13555-021-00588-8	2
Gutzmer R, Leiter U, Mohr P, et al. Interim analysis of the multinational, post-authorization safety study (NISSO) to assess the long-term safety of sonidegib in patients with locally advanced basal cell carcinoma. *BMC Cancer*. 2024;24(1):1401. doi:10.1186/s12885-024-13101-z	2
Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol*. 2018;32(3):372-381. doi:10.1111/jdv.14542	1
Lear JT, Morris LM, Ness DB, Lewis LD. Pharmacokinetics and pharmacodynamics of Hedgehog pathway inhibitors used in the treatment of advanced or treatment-refractory basal cell carcinoma. *Expert Rev Clin Pharmacol*. 2023;16(12):1211-1220. doi:10.1080/17512433.2023.2285849	3
Lewis K, Dummer R, Farberg AS, Guminski A, Squittieri N, Migden M. Effects of Sonidegib Following Dose Reduction and Treatment Interruption in Patients with Advanced Basal Cell Carcinoma During 42-Month BOLT Trial. *Dermatol Ther (Heidelb)*. 2021;11(6):2225-2234. doi:10.1007/s13555-021-00619-4	1
Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol*. 2015;16(6):716-728. doi:10.1016/S1470-2045(15)70100-2	1
Murgia G, Valtellini L, Denaro N, et al. Gorlin Syndrome-Associated Basal Cell Carcinomas Treated with Vismodegib or Sonidegib: A Retrospective Study. *Cancers (Basel)*. 2024;16(12):2166. doi:10.3390/cancers16122166	2
Nguyen A, Xie P, Litvinov IV, Lefrançois P. Efficacy and Safety of Sonic Hedgehog Inhibitors in Basal Cell Carcinomas: An Updated Systematic Review and Meta-analysis (2009-2022). *Am J Clin Dermatol*. 2023;24(3):359-374. doi:10.1007/s40257-023-00763-x	2
Odom D, Mladsi D, Purser M, et al. A Matching-Adjusted Indirect Comparison of Sonidegib and Vismodegib in Advanced Basal Cell Carcinoma. *J Skin Cancer*. 2017;2017:6121760. doi:10.1155/2017/6121760	2
Patel S, Armbruster H, Pardo G, et al. Hedgehog pathway inhibitors for locally advanced and metastatic basal cell carcinoma: A real-world single-center retrospective review. *PLoS One*. 2024;19(4):e0297531. doi:10.1371/journal.pone.0297531	3

Article	Level of Evidence
Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial. *Eur J Cancer*. 2017;86:334-348. doi:10.1016/j.ejca.2017.08.022	2
Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol*. 2015;72(6):1021-1026.e8. doi:10.1016/j.jaad.2015.03.021	1
Soon SL, Ibrahim SF, Arron ST. A randomized phase II study evaluating vismodegib as neoadjuvant treatment of basal cell carcinoma preceding Mohs micrographic surgery: results and lessons learned. *Br J Dermatol*. 2019;181(1):208-209. doi:10.1111/bjd.17623	2
Truong K, Peera M, Liu R, et al. Real-world data on the efficacy and safety of hedgehog pathway inhibitors in patients with basal cell carcinoma: Experience of a tertiary Australian centre. *Australas J Dermatol*. Published online October 25, 2024. doi:10.1111/ajd.14373	2
Villani A, Fabbrocini G, Costa C, Scalvenzi M. Sonidegib: Safety and Efficacy in Treatment of Advanced Basal Cell Carcinoma. *Dermatol Ther (Heidelb)*. 2020;10(3):401-412. doi:10.1007/s13555-020-00378-8	3
Villani A, Scalvenzi M, Micali G, et al. Efficacy and safety of sonidegib for the management of basal cell carcinoma: a drug safety evaluation. *Expert Opin Drug Saf*. 2023;22(7):525-531. doi:10.1080/14740338.2023.2227089	3

Table 2. *Consensus Statements and Clinical Recommendations for the Treatment of Locally Advanced Basal Cell Carcinomas With Hedgehog Inhibitors.*

Consensus Statement/Recommendation	Strength of Recommendation	Consensus Vote
HHIs are an effective treatment that can help reduce the tumor burden of locally advanced basal cell carcinomas as a primary or neoadjuvant therapy prior to Mohs or other interventions.	A	9/9
Sonidegib can be considered for patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation, individuals who are not good candidates for surgery or radiation, and/or patients with high burdens of BCCs including those with Gorlin syndrome.	A	9/9
It is recommended that 200 mg of sonidegib be taken daily, and duration and dose can be adjusted according to patient response and side effects.	B	9/9
The most common side effects associated with the use of hedgehog inhibitors include muscle cramps/spasms, alopecia, taste alterations, and fatigue.	A	9/9
Although both medications are hedgehog inhibitors, sonidegib has a different pharmacokinetic and pharmacodynamic profile, including longer half-life and increased tissue distribution, compared to vismodegib.	B	9/9
Sonidegib is associated with a lower rate and later mean onset of adverse events as compared to vismodegib.	C	9/9
For selected patients on hedgehog inhibitors, treatment interruption can allow patients to better tolerate the side effects while maintaining efficacy.	C	9/9
We recommend supplementation of between 1,000 to 2,000 mg of L-carnitine daily along with appropriate nutritional counseling when starting HHIs.	C	9/9
The efficacy of sonidegib and vismodegib is comparable, but critical evaluation is limited by the lack of head-to-head studies.	C	9/9

ing greater than 6 months.[15] At 30 months, the ORRs for laBCC were 56.1% (central review) and 71.2% (investigator review).[18] Lastly, in the 42-month follow-up study for patients on 200mg of sonidegib daily, the ORRs were 56% for laBCC (central review), 71% for laBCC (investigator review), and 8% for metastatic BCC with a 26.1-month median duration of response.[16] In the same study, an assessment of outcomes based on BCC subtype demonstrated an ORR of 59.5% for aggressive laBCC compared to 51.7% for nonaggressive types.[17] The ORRs were greatest for infiltrative and morpheaform BCCs among the aggressive subtypes.[17]

In a meta-analysis of 20 studies examining the efficacy of HHIs by Nguyen et al, the pooled ORR for HHIs was 64.9% for advanced BCC, demonstrating that the majority of patients achieved at least a partial response with treatment.[26] This strategy supports the use of HHIs as a neoadjuvant therapy to reduce tumor burden. In a study by Ally et al, 15 patients receiving neoadjuvant vismodegib experienced an average 27% surgical area defect reduction following a mean of four months of treatment.[38] In another study, 55 patients with facial BCCs that were inoperable or presented major functional and/or aesthetic risk were treated with neoadjuvant vismodegib, and 80% of patients showed downstaging (61% of which had a complete response) following treatment.[39] Improvement in tumor burden measured by total body videodermoscopy and dynamic optical coherence tomography was also demonstrated in 14 patients with difficult-to-treat BCCs on 200mg of sonidegib daily; 80% of participants achieved complete clearance and 75% had a reduction in tumor diameter.[22]

While larger scale studies are needed, there has been no evidence to date supporting the creation of skip lesions with the use of HHIs. In a randomized phase II study examining the use of vismodegib as neoadjuvant therapy prior to Mohs, two patients treated with placebo had skip lesions while none were seen in patients treated with vismodegib, suggesting that treated BCCs may reduce as discrete lesions.[29] Thus, the expert panel, in accordance with the FDA and a multidisciplinary European consensus panel, recommend the use of HHIs for advanced BCC as a primary or neoadjuvant therapy prior to surgical intervention.[40]

Statement 2: *Sonidegib can be considered for patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation, individuals who are not good candidates for surgery or radiation, and/or patients with high burdens of BCCs including those with Gorlin syndrome. (SORT Level A)*

Based on efficacy and safety in their clinical trials, the FDA approved sonidegib and vismodegib for the treatment of laBCC in patients who are not candidates for surgery/radiation therapy or have recurrent cancer following surgery/radiation.[26,34] The expert panel notes that other patient populations can also benefit from treatment consideration including patients who chose not to have surgery/radiation, are surgery fatigued after having multiple skin cancers and removals, or desire less postoperative scarring. Additionally, HHIs may be offered as a treatment modality for reduction in tumor size where surgery may have substantial functional and/or cosmetic implications.

The panel also recommends that HHIs be considered in patients with significant BCC tumor burden including patients with Basal Cell Nevus Syndrome (aka Gorlin syndrome). A meta-analysis of HHIs showed that seven Basal Cell Nevus Syndrome patients treated with sonidegib had an ORR of 85.7% and complete response rate of 42.9%; in 250 patients with Basal Cell Nevus Syndrome treated with vismodegib, the ORR was 70.1% and complete response rate was 49.3%.[26] In a retrospective review of 16 Gorlin syndrome patients, sonidegib demonstrated superior efficacy and safety in preventing tumor growth compared to vismodegib, with 61.5% of patients achieving clinical remission with four months of sonidegib treatment compared to 16.7% with vismodegib.[25] Thus, while sonidegib and vismodegib are both efficacious, the expert panel notes that sonidegib may be more efficacious for syndromic populations that have markedly increased BCC burdens.

Statement 3: *It is recommended that 200mg of sonidegib be taken daily, and duration and dose can be adjusted according to patient response and side effects. (SORT Level B)*

200mg of sonidegib daily for the treatment of laBCC is recommended in the package insert based on results from the BOLT trial showing similar efficacy between the 200mg and 800mg groups but fewer adverse events (AEs) and discontinuations at the lower dosage.[20] In a study by Lewis et al examining the ORRs of patients taking sonidegib 200mg daily with and without dosage reductions and interruptions, they found that response rates to treatment were similar despite dosage reduction (46.2% in those with at least one dose reduction or interruption versus 48.5% for those without either).[19]

Thus, patients requiring practical dosage reduction or interruption for laBCC therapy secondary to side effects may not have decreased treatment efficacy. Additionally, in an analysis of real-world clinical treatment of laBCC with sonidegib, dosing interruption to every other day resulted in better tolerability.[41] Of note, in a study by Patel et al, greater rates of dosage reduction (59% versus 24%) and medication discontinuation (30% versus 9%) were seen with vismodegib compared to sonidegib.[33]

The expert panel notes that extending the duration of treatment is key to improving response rates. The expert panel had variation in the specific dosing reduction strategies they use but agreed that clinicians should select dosing regimens after considering patient tolerance and feasibility for long-term disease control.

Statement 4: *The most common side effects associated with the use of hedgehog inhibitors include muscle cramps/spasms, alopecia, taste alterations, and fatigue. (SORT Level A)*

Although they are efficacious, HHIs are associated with a relatively high rate of AEs, which are the primary cause of treatment discontinuation.[23,26] In a post hoc analysis of the trials of sonidegib and vismodegib, the rates of muscle spasms were 54.4% versus 70.6% (p=0.02), 49.4% versus 58% for alopecia, 44.3% versus 70.6% (p=0.0003) for dysgeusia, and 32.9% versus 19.3% (p=0.0429) for fatigue.[23] Results from real-world studies on the use of sonidegib support muscle spasms as being the most common side effect and show that the rates of most AEs are lower than those seen in the pivotal trials.[30,35] Majority of the AEs seen were grades 1-2, with two patients reported to have grade 3 muscle spasms and one patient with grade 3 fatigue for both sonidegib and vismodegib; there were no grade 3-4 AEs seen for dysgeusia or alopecia for either drug.[23] Gastrointestinal

AEs, such as diarrhea, nausea, and weight loss, were common with HHIs and seen at rates greater than 15% but were less frequent than the AEs noted above. The side effects listed in this consensus statement have anecdotally been observed by the expert panel most frequently in clinical practice, and they recommend counseling patients on expectations and management of side effects to prevent premature discontinuation.

In addition to dosing interruption and/or alteration, pharmacologic and counseling interventions should be taken to address AEs that occur while on treatment.[42] Some of the strategies proposed by Bossi et al to maximize efficacy and tolerability while on HHI therapy for longer periods include the initiation of oral or topical minoxidil and finasteride for alopecia, dietary counseling and zinc gluconate supplementation for dysgeusia, adequate hydration and amlodipine for muscle cramps, and methylphenidate for fatigue.[42] The expert panel concurs that several interventions exist that can make HHI treatment tolerable and promote increased efficacy.

Of note, monitoring of creatinine phosphokinase and creatinine levels is advised for HHIs per the FDA prescribing information.[35] Elevations in creatine kinase and creatinine levels were seen more frequently with sonidegib than vismodegib.[26] The expert panel agrees that creatinine phosphokinase elevations generally occur in the setting of severe muscle spasms, and clinical recognition of this symptom should prompt laboratory assessment. Additionally, HHIs are teratogenic and must not be given to women who are pregnant or have childbearing potential. Similarly, men can transmit HHIs through semen and must avoid fathering children for several months after treatment has ended.[35]

Statement 5: *Although both medications are hedgehog inhibitors, sonidegib has a different pharmacokinetic and pharmacodynamic profile, including longer half-life and increased tissue distribution, compared to vismodegib. (SORT Level B)*

Despite having similar pharmaceutical properties, sonidegib and vismodegib have pronounced differences in pharmacodynamics. Examinations of volumes of distribution for both drugs found the volumes of distribution of sonidegib to be greater than 9,000L compared to 16-27L for vismodegib, likely secondary to sonidegib being more lipophilic, suggesting that sonidegib penetrates tissues and skin to a greater degree than vismodegib, which may allow for increased tumor response.[32] Additionally, vismodegib demonstrated less affinity for binding plasma and proteins and has a half-life in cancer patients that is seven times shorter than that of sonidegib.[32] The expert panel hypothesizes that the differences in the pharmacological profiles between the therapies may help explain some of the differences in side effect profile seen in clinical practice. This is corroborated by case reports demonstrating better tolerance and efficacy with sonidegib treatment in certain patients who had been treated with vismodegib.[43]

Statement 6: *Sonidegib is associated with a lower rate and later mean onset of adverse events as compared to vismodegib. (SORT Level C)*

A lack of head-to-head trials make direct comparison difficult, but the post-hoc analysis data reviewed above showed significantly lower rates of muscle cramps and dysgeusia and higher rates of fatigue with sonidegib treatment compared to vismodegib.[23] In the meta-analysis of HHIs by Nguyen et al, the rates of muscle cramps, alopecia, and dysgeusia were all lower with sonidegib than with vismodegib, but statistically significant differences were not determined.[26] Importantly, the mean time to onset of AEs was greater with sonidegib than vismodegib; the time to onset of muscle spasms was 2.1 months for sonidegib versus 1.2 months for vismodegib ($p=0.003$), 5.5 months versus 2.9 months for alopecia ($p=0.001$), and 3.7 months versus 1.4 months for dysgeusia ($p<0.0001$).[23] There were statistically significant differences in the time to onset for all AEs analyzed except for fatigue and weight loss.[23]

The expert panel emphasized the potential importance of these findings for clinical practice, as a greater delay in the onset of AEs provides more opportunity for efficacy and sustained clinical response before having to initiate dose reduction/interruption. They note that this aspect of the side effect profile also strengthens the clinical utility of sonidegib as neoadjuvant therapy.

Statement 7: *For selected patients on hedgehog inhibitors, treatment interruption can allow patients to better tolerate the side effects while maintaining efficacy. (SORT Level C)*

There is evidence to support the efficacy of HHIs despite treatment interruptions; in the MIKIE trial for vismodegib, which examined intermittent dosing efficacy, patients who were off treatment for 24 weeks between periods of dosing still had high rates of tumor clearance.[14] In addition, recommendations from other expert clinicians corroborate the use of treatment interruption to maintain long-term clinical efficacy while limiting side effect incidence.[35,44]

The expert panel states that drug holidays are a common and useful strategy for mitigating AEs associated with HHIs and can prolong the duration for which patients can tolerate therapy. They recommend for patients who will require extended treatments due to significant local disease or high overall tumor burdens (Gorlins syndrome and BCNS) that dose modifications and interruptions be implemented earlier to proactively extend treatment duration.

Statement 8: *We recommend supplementation of between 1,000-2,000mg of L-carnitine daily along with appropriate nutritional counseling when starting HHIs. (SORT Level C)*

Levocarnitine (L-carnitine), a nonessential amino acid stored in muscle tissue, is effective in reducing the incidence of muscle spasms with HHIs.[13,31] A case series of three patients suffering from severe muscle spasms while taking vismodegib demonstrated a substantial improvement in their perceived severity of muscle spasms,

allowing them to continue treatment without discontinuation, with L-carnitine doses between 1,500-2,000mg.[31] In a double-blind, randomized, placebo-controlled, two-period cross-over study, 8 patients being treated with vismodegib started on L-carnitine supplementation and were found to have their median muscle spasm frequency decreased by 48.1% (p=0.02), resulting in an effect size of -137% between L-carnitine and placebo.[31] Study participants also had a decreased median number of body locations affected by muscle spasms.[31]

The experts recommend starting L-carnitine supplementation two weeks prior to initiation of HHIs, and even earlier for vismodegib to prevent cramping. Additionally, they state that nutritional counseling that includes discussion of hydration is important for encouraging appropriate water intake, as dysgeusia can contribute to dehydration, which may worsen muscle cramping.

Statement 9: *The efficacy of sonidegib and vismodegib is comparable, but critical evaluation is limited by the lack of head-to-head studies. (SORT Level C)*

Given that there are no head-to-head trials comparing sonidegib and vismodegib, the differences in their design and assessment must be considered when interpreting efficacy and safety. One key difference in their pivotal trials was reporting criteria; the ERIVANCE trial for vismodegib utilized RECIST to assess treatment response while the BOLT trial for sonidegib used modified RECIST, which incorporated imaging and histological interpretation and is generally acknowledged as being more stringent.[27] In a study by Odom et al where the results of the two studies were compared following a matching adjustment to account for discrepancies in the baseline patient characteristics, the post-matched ORR for sonidegib was 56.7% with a median-progression free survival of 22.1 months compared to 47.6% and 9.5 months for vismodegib.[27] In a similar study, Dummer et al assessed the data from the BOLT study using RECIST like criteria and found a 18-month ORR of 60.6% with sonidegib use compared to a 21-month ORR of 47.6% with vismodegib.[45] Additionally, the median duration of response for sonidegib was longer than that of vismodegib, at 26.1 months at 30 months, but an adjusted analysis of complete response rates for sonidegib and vismodegib found them to be similar.[45] In contrast, a meta-analysis of HHI efficacy found the ORRs of vismodegib and sonidegib to be 68.5% and 50.1%.[26] The experts contend that the difference in data assessment makes comparison difficult, but both HHIs likely have similar efficacy although sonidegib is better tolerated.

Conclusion

Following a comprehensive review of the literature, the expert consensus panel crafted nine consensus statements regarding the efficacy, safety, and administration of HHIs that may help guide clinicians in treating applicable patients. Sonidegib and vismodegib have proven and similar efficacy in treating laBCC, but sonidegib has lower rates and delayed time of onset of AEs compared to vismodegib, which may allow for improved disease control. There are key pharmacokinetic and pharmacodynamic differences between sonidegib and vismodegib, but L-carnitine supplementation and dosage interruption can be appropriate for both therapies. Overall, HHIs provide a useful therapeutic option in the treatment of advanced BCC that should be considered by clinicians with these guiding statements in mind.

Potential conflicts of interest

Mohammed Dany, MD, PhD, is on the Speakers Bureau for Castle Biosciences and Sun Pharma. Scott Dinehart, MD, is a speaker and consultant for SUN Pharma and Genentech. Mark Lebwohl is an employee of Mount Sinai; receives research funds from Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen, Pfizer, Sanofi-Regeneron, and UCB; and serves as a consultant for Almirall, AltruBio Inc., Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda,Trevi, and Verrica. Jesse Lewin, MD, is a consultant for SUN Pharma. George Monks, MD, is a consultant for SUN Pharma. Michael Mortazie, DO, is a speaker for SUN Pharma. Todd Schlesinger, MD, is a speaker, consultant, and/or investigator for AbbVie, Almirall, Apogee, Arcutis, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Eli Lilly and Company, Flint Clinical, Genentech, Janssen, LEO Pharma, Pfizer, Regeneron, SUN Pharma, and UCB Pharma; has served as an investigator for AbbVie, Allergan, Arcutis, ASLAN Pharmaceuticals, Biofrontera, Boehringer Ingelheim, Cara Therapeutics, Castle Biosciences, ChemoCentryx, Coherus Biosciences, Concentrics, Concert Pharmaceuticals (Now SUN), Cutanea, Dermavant, Eli Lilly and Company, Galderma, Highlitll, Incyte Corporation, Janssen, Nimbus Therapeutics, Novartis, Processa, Prolacta, Regeneron, Sanofi, Takeda, Trevi Pharmaceuticals, and Verrica; is a shareholder of Bristol Myers Squibb, Eli Lilly and Company, Greenway Therapeutix, and Remedly; and serves as a consultant for Beiersdorf, MJH Life Sciences, RBC Consultants, HTL Biotechnology, L'Oreal, and Dermsquared. Shannon Trotter, DO, has received research support and/or served on the Speakers Bureau for Castle Biosciences, Sun Pharma, Pfizer, Verrica Pharmaceuticals, Amgen, Acelyrin, Insmed, Vyne, AbbVie; and is a consultant for Sun Pharma. Darrell Rigel, MD, is a consultant for SUN Pharma.

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