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Skin Cancer (T Ito, Section Editor)

Sonic Hedgehog Pathway Inhibition in the Treatment of Advanced Basal Cell Carcinoma

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Opinion statement

Advanced basal cell carcinoma (BCC) represents a small proportion of BCCs that are not amenable to standard therapies due to lack of efficacy, high recurrence risk, and excessive morbidity. Implication of the Sonic hedgehog (Shh) pathway in the development of BCC has led to the development of systemic Shh pathway inhibitors, providing patients with advanced BCCs new treatment options and improved survival. There are currently two Food and Drug Administration (FDA)–approved Shh inhibitors, vismodegib and sonidegib, for advanced basal cell carcinomas. Vismodegib has approval for locally advanced BCCs (laBCC) and metastatic BCC (mBCC), while sonidegib has approval for laBCC. These agents have also been used for prevention in nevoid basal cell carcinoma syndrome and as neoadjuvant therapy before surgery, and we feel that there is a growing role of Shh inhibitors in these settings. Head-to-head randomized controlled trials comparing vismodegib to sonidegib are lacking. Adverse events can limit the utility of these medications by leading to treatment discontinuation in a large proportion of patients, and it is thus essential that prescribers be able to anticipate and manage the most frequent side effects of muscle spasms, alopecia, dysgeusia, nausea, and weight loss. Other Shh inhibitors, including the antifungal itraconazole, have been investigated in small trials, but further research is needed before recommending their routine clinical use. Additionally, there are several new agents under investigation that may have improved efficacy for resistant

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tumors by utilizing different mechanisms of action than the two currently approved medications.

Introduction

Basal cell carcinoma (BCC) is the most common type of human malignancy and comprises about 80% of nonmelanoma skin cancer [1]. In the USA, there are over 2.8 million new cases diagnosed each year and the incidence continues to rise [1]. Despite the high prevalence of BCC, mortality from the disease remains low. The significant majority of BCCs remain localized to the skin and are most commonly treated with surgical procedures such as standard excision, curettage and electrodessication, or Mohs micrographic surgery. Radiation therapy can also be utilized as primary treatment when surgery is contraindicated or the patient is not amenable, or as adjuvant treatment in certain high-risk patients. Additional superficial treatments have utility in select situations and include photodynamic therapy (PDT), intralesional injections (5-fluorouracil or bleomycin), and topical therapies (such as imiquimod or 5-fluorouracil). However, approximately 1% of patients with BCC develop advanced disease and may have minimal efficacy or significant morbidity from standard therapies [2].

Pathogenesis of basal cell carcinoma

Ultraviolet (UV) radiation is the greatest risk factor for the development of nonmelanoma skin cancer. Episodes of intense sun exposure and resulting sunburns appear to be the primary risk for developing BCC, as opposed to the cumulative UV exposure that is a major risk factor for squamous cell carcinoma (SCC) [3].

Basal cell carcinoma has unique growth requirements, as it is reliant on a specific connective tissue stroma. It is hypothesized that the characteristic indolent nature and low rate of metastasis are due to this unconditional dependence on growth factors produced by fibroblasts in its stroma.

The role of the Hedgehog pathway in basal cell carcinoma

Research into the genetics of nevoid basal cell carcinoma (NBCC) syndrome (Gorlin-Goltz syndrome) has provided insight into the molecular pathogenesis of BCC, most importantly the critical involvement of Hedgehog (Hh) signaling pathway in driving tumorigenesis. The human Hedgehog pathway is complex, with three identified *hedgehog* genes (*Sonic hedgehog* (*SHH*), *Desert hedgehog* (*DHH*), and *Indian hedgehog* (*IHH*)) and two *patched* genes (*PTCH1* and *PTCH2*). The downstream effects of the Hh pathway are primarily exerted by proteins encoded by the *glioblastoma* (*GLI*) family of genes with resultant increase in proliferation and inhibition of apoptosis. In human skin, the Sonic hedgehog (Shh) signaling pathway plays an integral role in the differentiation and proliferation of hair follicles and sebaceous glands, as well as the maintenance of stem cell populations [4].

NBCC syndrome is a rare autosomal dominant condition in which a non-functional copy of *Ptch1* is either inherited or acquired through a germline mutation. It is associated with characteristic developmental defects such as odontogenic keratocysts, calcification of the falx cerebri, palmoplantar pits, neurologic defects, and skeletal abnormalities [5]. There is also a significant propensity for neoplasia, with patients developing numerous basal cell carcinomas, predominantly in sun-exposed areas, as well as medulloblastomas, ovarian fibromas, and cardiac fibromas.

The vast majority of human BCCs are sporadic and, like NBCC syndrome, are similarly driven by the Hedgehog signaling pathway. Genetic analysis has shown *Ptch1* to be the most frequently mutated gene in sporadic BCCs, with up to 80% demonstrating loss of function in at least one allele and the remainder having activating downstream mutations in the *SMO* gene [6]. The second most common mutation in sporadic BCCs is in the p53 tumor suppressor gene. Interestingly, those with inherited mutations in p53 (Li-Fraumeni syndrome) have a significantly increased risk of multiple malignancies but do not have an increased propensity to develop BCCs, suggesting that p53 mutations may be a secondary event and not necessary for tumorigenesis [7].

Advanced basal cell carcinoma

Advanced BCCs fall into two categories, locally advanced BCC (laBCC) and metastatic BCC (mBCC). LaBCC includes primary tumors that invade surrounding structures (i.e., cartilage, bone, muscle, or local lymph nodes). Management of laBCC can be challenging, as surgery can have a high risk of recurrence or result in significant morbidity from functional or esthetic impairment. The utility of radiation therapy for laBCC is often limited due to high recurrence risk, prior radiation failure, sensitivity to radiation, or limited access to treatment.

Metastatic BCC is defined as spread to distant sites from the primary tumor and occurs most commonly to the lymph nodes, lungs, and bone. The incidence of metastatic BCC is exceedingly rare (0.0028–0.5%) and typically evolves from large, ulcerated, locally invasive cases subjected to prolonged neglect or avoidance of medical care [8]. Metastatic BCC has a poor prognosis with reported median survival time of approximately 8 months when signs of nodal metastases are present [9].

Until recently, there were few treatment options for patients with laBCC and mBCC. New BCC-targeted treatments that inhibit the Hh pathway have demonstrated significant efficacy in treating advanced BCC and have revolutionized the management of these patients.

Sonic hedgehog inhibition in the treatment of basal cell carcinoma

Smoothened inhibitors

Vismodegib

Vismodegib (Erivedge®) is an orally dosed, second-generation cyclopamine derivative that acts by binding directly to SMO, inhibiting its function in

downstream Shh signal transduction. It was approved by the FDA in January 2012 as the first-in-class Shh pathway inhibitor for the treatment of laBCC and mBCC [10]. Approval was based on the pivotal phase II study ERIVANCE, a multicenter study of 104 patients with two treatment cohorts: unresectable laBCC and mBCC (Table 1) [11]. A control group was not assigned. Based on phase I safety data, all patients received vismodegib 150 mg daily. The primary endpoint was the objective response rate (RR). A response in laBCC was defined as ≥ 30% tumor size reduction or complete resolution of tumor ulceration (if present at baseline). A response in mBCC was defined as ≥ 30% decrease in sum of longest diameter of target lesions. Efficacy analysis by independent review of the laBCC group ($n = 63$) revealed an RR of 43% (95% CI, 31–56) and in the mBCC group ($n = 33$) an RR of 30% (95% CI, 16–48). Investigator-assessed RRs were higher with a RR of 60% (95% CI, 47–72) for laBCC and 46% for mBCC (95% CI, 28–62). A complete response (absence of residual BCC on analysis of a biopsy specimen) was observed in 21% of the laBCC. These response rates were found to be durable, with similar RRs of 60% in laBCC and 49% in mBCC at the final 39-month follow-up analysis [12].

Since the initial ERIVANCE trial, additional clinical trials have provided additional efficacy and safety data [13•, 14, 15••]. The largest trial to date, the STEVIE trial, was a single-arm multicenter study that treated 1215 patients with either laBCC ($n = 1119$) or mBCC ($n = 96$) with vismodegib 150 mg daily

Table 1. Review of the two FDA-approved Shh inhibitors for advanced BCC

	Vismodegib	Sonidegib
Dosing	150 mg daily	200 mg daily
FDA-approved indications	laBCC mBCC	laBCC
Notable clinical trials	ERIVANCE (pivotal trial): 104 patients treated with vismodegib 150 mg daily Objective RRs were 60% for laBCC and 45% for mBCC at 39-month follow-up. STEVIE (largest trial): 1215 patients treated with vismodegib 150 mg daily RRs were 69% for laBCC and 37% for mBCC at median 18-month follow-up.	BOLT (pivotal trial): 230 patients randomized 1:2 to 200 mg daily or 800 mg sonidegib daily RRs in 200 mg arm were 56% for laBCC and 7% for mBCC at 30-month follow-up.
Most common adverse events	Muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, anorexia, diarrhea	Muscle spasms, alopecia, dysgeusia, nausea, diarrhea, weight loss, elevated creatinine kinase (CK), fatigue
Required lab monitoring	Pregnancy test before starting; contraception for females during therapy and 24 months following; contraception for males during therapy and 3 months following Other lab monitoring not required; creatinine kinase (CK) can be checked per physician discretion	Pregnancy test before starting; contraception for females during therapy and 20 months following; contraception for males during therapy and 8 months following CK and creatinine at baseline and periodically during treatment and as indicated

for a median duration of 8.6 months. Investigator-assessed RRs were 69% (95% CI, 66–71) for patients with laBCC and 37% (95% CI, 27–48) for those with mBCC. These numbers were consistent with the investigator-assessed RRs in the ERIVANCE study but higher than the independently-assessed RRs.

Sonidegib

Sonidegib (Odomzo®) is an orally dosed SMO inhibitor that is structurally distinct from vismodegib. It was approved by the FDA in June 2015 for treatment of laBCC that has either recurred following surgery or radiation therapy or in patients who are not candidates for surgery or radiation [16]. Approval and the majority of efficacy and safety data came from the multicenter phase II BOLT trial of patients with mBCC or laBCC not amenable to surgery or radiation [17–19]. Patients were randomized in a 1:2 ratio to receive either 200 mg (lowest active dose; $n = 79$) or 800 mg (maximum tolerable dose; $n = 151$) of sonidegib daily. The primary endpoint was an objective RR in both treatment arms. Objective RR in the 200-mg group was 43% for laBCC and 15% for mBCC, and in the 800-mg group was 38% for laBCC and 17% for mBCC. No additional efficacy was found from 800-mg dosing over the 200-mg dose. At 30-month follow-up, objective RRs in the 200-mg group were sustained at 56% for laBCC and 7% for mBCC [19•]. The 200-mg dose also exhibited a more benign side effect profile, with a lower rate of grade 3/4 adverse events (43% vs 64% at long-term follow-up) and adverse events leading to discontinuation of the drug.

Head-to-head randomized controlled trials comparing vismodegib to sonidegib are lacking. Vismodegib appears to be the treatment of choice for mBCC, as it has explicit FDA approval for this indication and seems to have superior efficacy to sonidegib in treating mBCC based on indirect comparison of response rates. Some comparisons suggest that vismodegib has higher efficacy for laBCC as well and lower rates of gastrointestinal side effects [20], but it is difficult to draw firm conclusions without head-to-head trials. In particular, some authors note that the more stringent response criteria used in the BOLT trial for sonidegib (modified RECIST) preclude direct comparison with the major vismodegib trials that employed the RECIST1 criteria [21].

Side effects from SMO inhibitors

Side effects from SMO inhibitors are frequent and can be significant. The side effect profile is often the limiting factor in continued treatment and should be weighed with the drug's potential benefits. In the initial ERIVANCE study of vismodegib, all patients reported a treatment-related adverse event, although the majority of these were low grade (ranked mild to moderate) in severity. The most frequently encountered side effects were muscle spasms (68%), alopecia (63%), dysgeusia (51%), weight loss (46%), fatigue (36%), nausea (29%), anorexia (23%), and diarrhea (22%). Of note, the high rates of alopecia and dysgeusia are considered to be on-target effects due to the inhibition of normally active Shh signaling in hair follicles and taste buds.

Subsequent data from additional trials have found similar side effect profiles to the ERIVANCE study. In the STEVIE trial, 98% of patients had at least one adverse event with a similar profile to the EVIRANCE trial. The most frequent

adverse events were muscle spasms (66%), alopecia (62%), dysgeusia (55%), weight loss (41%), anorexia (25%), and fatigue (24%). The safety profile was similar regardless of NBCC syndrome status. There were 46 deaths (3.8%) during the study; seven were considered treatment-related by the investigator but the drug safety monitoring board deemed all deaths unrelated to treatment or insufficient to determine. A subsequent exploratory analysis of a cohort of 266 patients found that the majority of side effects resolved by 12-months after drug discontinuation. Muscle spasms were the first to resolve within 1–3 months, followed by dysgeusia and alopecia by 6 months. Weight loss was slower to resolve but improved in most patients by 12-month follow-up.

The side effect profile for sonidegib is similar to that of vismodegib. The most frequently reported adverse events with sonidegib 200 mg daily at long-term follow-up were muscle spasms (54%), alopecia (49%), dysgeusia (44%), nausea (39%), diarrhea (32%), weight loss (30%), elevated creatinine kinase (CK) (30%), fatigue (30%), and anorexia (23%). An increased frequency of these adverse events was observed in the 800-mg dose group. Elevated CK and rhabdomyolysis were the most common serious AEs, with incidences of 2.6% each.

Some data has suggested a seemingly paradoxical increased risk for developing cutaneous SCC in patients treated with vismodegib. A case-control study of 55 patients and 125 controls demonstrated a hazard ratio of 8.12 (95% CI, 3.89–16.97) for the risk of developing SCC [22]. However, a recent retrospective cohort study compared rates of cutaneous SCC among patients with BCCs treated with vismodegib versus patients with BCCs treated with conventional therapies [23]. The vismodegib-treated group came from historic data and included 556 patients from the STEVIE, ERIVANCE, and two small phase I clinical trials. The control group included 1119 patients from a cohort of nonmelanoma skin cancer patients at the authors' institution. The analysis did not find an increased risk of cutaneous SCC with the use of vismodegib, with a hazard ratio of 0.57 (95% CI, 0.28–1.16). The major limitation of this study was the use of historic data for the vismodegib group. It is postulated that the initial data suggesting an increased risk of SCC with vismodegib use may have been confounded by the increased frequency of skin screenings in patients on clinical trials, but future placebo-controlled trials are needed to more accurately elucidate the SCC risk.

Management of SMO inhibitor adverse events

Treatment-associated adverse events, even those that are low grade, can lead to treatment discontinuation in a large percentage of patients. In the STEVIE trial, 31% of patients discontinued vismodegib due to adverse events [15••]; in the BOLT trial, even in the lower-dosed 200-mg group, 22% of patients discontinued sonidegib due to adverse events [17]. It is thus essential that physicians be able to appropriately anticipate and manage side effects from SMO inhibitors.

A management algorithm has been proposed for the most common side effects of muscle spasms, dysgeusia, alopecia, weight loss, and fatigue [24•]. For grade 3 or higher symptoms in any category, therapy should be interrupted for at least 2–4 weeks or the dosing regimen should be tailored. Grade 1 or 2 muscle spasms can be alleviated with non-pharmacologic interventions such as passive stretching, heating or cooling therapy, and massage, or with

pharmacologic agents such as calcium channel blockers. For patients on sonidegib, per the package insert a serum CK level should be checked before initiating treatment and periodically during treatment as clinically indicated. Checking CK levels is not required in patients on vismodegib but can be checked per physician judgment. Nutritional support and meal modifications such as the addition of flavor enhancers and cooling foods are the mainstays of managing dysgeusia and weight loss; zinc supplementation or tetrahydrocannabinol (THC) can be considered. Topical minoxidil is recommended as first-line to alleviate symptoms of alopecia.

Vismodegib caused severe fetal malformations and deaths in animal studies at lower exposures than the approved human dose of 150 mg daily. Thus, all women of child-bearing potential should utilize two forms of conception during therapy and for 24 months after the final dose [25]. As the medication is secreted in semen, male patients should use protection during therapy and for 3 months after the final dose. Vismodegib may cause amenorrhea and infertility; thus, fertility preservation strategies can be discussed with both male and female patients prior to initiating treatment.

SMO inhibitors in NBCC syndrome

Although some of the aforementioned trials included NBCC patients, there are limited studies examining the use of systemic Shh inhibitors specifically in this patient population. One randomized, double-blinded, placebo-controlled study examined the use of vismodegib in the treatment of 41 patients with NBCC syndrome. The analysis found that the rate of new BCCs per patient per year decreased significantly after 3 months of vismodegib (2 vs 29, $p < 0.001$), and the size of pre-existing BCCs decreased as well (– 65% vs 11%, $p = 0.003$) [26]. Side effects in the NBCC patients were significant, resulting in 54% of patients discontinuing treatment. Upon cessation of vismodegib, nearly all of the BCCs that regressed while on therapy subsequently recurred. Follow-up analysis at 36 months that included results from a subsequent open-label phase demonstrated significantly fewer new BCCs per year when placebo patients ($n = 11$) were allowed to cross over to vismodegib (0.4 vs 30, $p < 0.0001$). The subsequent analysis also found that there were fewer new BCCs in patients who took vismodegib continuously than in those with interrupted dosing [27].

As side effects from continuous use of vismodegib are often prohibitive, a randomized, double-blind phase 2 study assessed two intermittent vismodegib dosing regimens in patients with multiple BCCs, including those with NBCC syndrome [13•]. Patients enrolled in the trial had six or more BCCs that were not locally advanced or metastatic. Enrollees were assigned 1:1 to receive one of two intermittent dosing schedules: 150 mg daily for 12 weeks alternating with 8 weeks of placebo for a total of four rounds of vismodegib (group A, $n = 116$), or 150 mg daily for 24 weeks (a more intense induction phase) followed by three rounds of 8 weeks of placebo followed by 8 weeks of 150 mg vismodegib daily (group B, $n = 113$). The primary endpoint of percent reduction in the number of clinically evident BCCs at the end of the 73-week study period was 63% (95% CI, 53–72) in group A and 54% (95% CI, 44–64) in group B. The rate of discontinuation due to adverse events was 23%, which was lower than the 54% in the aforementioned study that used continuous vismodegib dosing. However,

a lack of head-to-head trials comparing intermittent and continuous vismodegib regimens precludes definitive comparisons of tolerability.

Although the results from these trials suggest that vismodegib has efficacy at preventing and treating BCCs in NBCC syndrome and that intermittent dosing regimens may enhance tolerability, there are still no clear guidelines for use of vismodegib for long-term prevention of BCC in this setting.

Topical SMO inhibitors

One double-blind, vehicle-controlled, intraindividual study of 8 NBCC patients with 27 BCCs were randomized to twice daily treatment of either 0.75% sonidegib cream or vehicle [28]. Out of the 13 lesions treated with topical sonidegib, there was complete response in 3 lesions and partial response in 9, compared with only 1 partial response out of the 14 lesions treated with placebo. In vitro studies have investigated the penetration of topical vismodegib but there have not yet been any clinical studies utilizing a topical formulation of this agent [29, 30]. There are presently no topical SMO inhibitors available for commercial use.

Neoadjuvant use of SMO inhibitors for locally advanced BCC

SMO inhibitors have potential utility as a neoadjuvant treatment to surgery for laBCCs, but evidence for their use is not yet well established in this setting. Advantages of neoadjuvant SMO inhibition followed by surgical treatment include transient exposure to poorly tolerated SMO inhibitor side effects and the potential to decrease post-surgical defect size. A small, open-label study evaluated the use of vismodegib 150 mg daily for 3 to 6 months to decrease tumor size in high-risk BCCs prior to surgery [31]. There was a dropout rate of 29% due to side effects of vismodegib. Of patients who completed adjuvant treatment (average 4-month duration), there was a reduction of surgical defect size by 27% (95% CI, − 45.7 to − 7.9%, $p = 0.006$). After a mean follow-up of 11.5 months, recurrence was observed in one patient who was being treated for a previously recurrent infiltrative BCC and did not complete a full course of vismodegib. Subsequent open-label studies and case series provide further support to the utility of vismodegib as a neoadjuvant therapy, particularly for BCCs at high risk for functional or esthetic compromise with initial surgery [32–34].

Resistance to SMO inhibitors

Despite the significant clinical response of many advanced BCCs to SMO inhibitors, approximately 5–10% of patients demonstrate primary resistance with progression and no response. In patients who do respond, long-term efficacy is often mitigated by the development of tumor-acquired resistance to these medications. This phenomenon was first described in a case series that demonstrated regrowth of at least one tumor in 21% of patients with advanced BCC after a mean of 56 weeks [35]. Several potential mechanisms of resistance have been proposed and studied in mouse models. These mechanisms include point mutations in SMO [36, 37], amplification of *GLI* genes allowing tumors to escape SMO inhibition [38], identity switching to more closely resemble

stem cells of the isthmus [39], and the reduction of primary cilia, leading to a switch from the Shh pathway to Ras/MAPK pathway [40].

Additional Hedgehog pathway inhibitors

Alternate SMO inhibitors

Itraconazole, an FDA-approved antifungal, has been shown to inhibit the Shh pathway by blocking SMO migration to the tip of the primary cilium, a mechanism distinct from vismodegib and sonidegib [41]. Itraconazole has been shown to effectively inhibit *GLI* expression in vitro in cells with particular vismodegib-resistant mutations [42]. These investigators also demonstrated that in vitro treatment with both itraconazole and arsenic trioxide (which target different loci in the Shh pathway) cumulatively inhibited all other known SMO mutants. These findings suggest combination therapies targeting more than one component of the Shh pathway may be more effective in combating resistance.

A small, open-label, phase II clinical study treating 19 BCC patients with itraconazole alone was performed and found a reduction in GLI mRNA by 65% and a reduced tumor area of 24%; patients previously treated with vismodegib did not show significant changes in tumor size or proliferation [43]. Another small clinical study of 5 patients with mBCC resistant to typical SMO inhibitors found that combination treatment with itraconazole and arsenic trioxide decreased *GLI* mRNA expression by 75% [44]. The best clinical responses observed were stable disease; no regression of tumors occurred. The authors concluded that the scheduling and dosing in the study may not have been frequent or high enough to obtain maximal inhibition of the Shh pathway. In one case report, an advanced laBCC that involved sinuses and brain failed 6 months of vismodegib but responded to 3 months of sonidegib 200 mg daily and itraconazole pulses. This observation further supports the hypothesis that combination treatment with different agents targeting the Shh pathway may provide clinical benefit, and suggests that some patients may benefit from other agents within the same class.

Further studies are needed to better evaluate ideal dosing and the efficacy of itraconazole in the treatment of BCCs in humans. A clinical trial assessing the use of topical itraconazole to treat BCCs is in phase I of investigation [45]. Posaconazole, a second-generation triazole with fewer drug-drug interactions, was shown to inhibit the Shh pathway in vitro but there have not yet been any clinical studies looking at this agent [46].

GLI inhibitors

GLI transcription factors are the terminal effectors in Shh pathway signaling. Direct targeting of GLI may be a potentially ideal target in the treatment of advanced BCCs, especially in the context of SMO inhibitor resistance.

Arsenic trioxide (ATO) is a chemotherapeutic agent that is FDA approved for the treatment of promyelocytic leukemia [47]. ATO has been found to inhibit the Shh pathway by binding directly to GLI1 and GLI2 [48]. It has also been found to prevent the accumulation of GLI in the primary cilium, a necessary step for downstream Shh signaling [49]. There have been some studies exploring ATO in combination with itraconazole for the inhibition of GLI and treatment of BCC, as described above.

Direct GLI antagonists, or GANTs, are small molecules that inhibit GLI-mediated gene transcription [50]. Two such molecules are GANT-58 and GANT-61, but neither has been evaluated for Shh pathway inhibition in BCC and has yet to be tested in clinical trials for cancer. Several other agents that modulate the GLI pathway such as through PKA activation, interference with ciliogenesis, or inhibition of bromodomain and extra terminal (BET) proteins are under laboratory investigation [45].

Future directions

The discovery of the Shh pathway and its role in the pathogenesis of basal cell carcinoma has led to the development of novel therapies. The development of SMO inhibitors has been a significant milestone in the targeted treatment of malignancy, offering major improvements in morbidity and mortality in many cases of advanced BCC. Although several large clinical trials have highlighted the efficacy and relative tolerability of these agents, there is significant room for further research. Head-to-head trials comparing the two FDA-approved SMO inhibitors are lacking, as are controlled trials evaluating intermittent dosing regimens that may enhance compliance. Further evaluation of these medications as neoadjuvant therapies to surgery and as preventative treatments in NBCC syndrome is warranted. Although the multiple mechanisms of SMO inhibitor resistance convey challenges to treatment, continued research and further understanding may lead to improved systemic treatment strategies. Combination therapies may become especially relevant in the context of managing drug resistance in advanced BCC.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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