

# Investigational agents in metastatic basal cell carcinoma: focus on vismodegib

Nicolas Batty<sup>1</sup>  
Ellen Kossoff<sup>2</sup>  
Grace K Dy<sup>1</sup>

<sup>1</sup>Department of Medicine, Roswell Park Cancer Center, Buffalo, NY, USA;

<sup>2</sup>Department of Pharmacy, Roswell Park Cancer Center, Buffalo, NY, USA

**Abstract:** Vismodegib (GDC-0449, 2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide, Erivedge™) is a novel first-in-human, first-in class, orally bio-available Hedgehog pathway signaling inhibitor of the G-protein coupled receptor-like protein smoothed (SMO) which was approved in the United States on January 2012. This signaling pathway is involved in the carcinogenesis of several types of tumor, as exemplified by basal cell carcinoma. This review focuses on the role of the Hedgehog pathway in the pathogenesis of basal cell carcinoma, the pharmacology and the clinical activity of vismodegib, as well as a brief summary of investigational agents in development targeting this pathway.

**Keywords:** hedgehog inhibitors, metastatic basal cell carcinoma, hedgehog signalling pathway

## Background

Basal cell carcinoma (BCC) is the most common human malignancy.<sup>1</sup> Fortunately, BCC rarely becomes metastatic. Most of the 1 million cases per year in the United States are localized and treated with surgical excision.<sup>2</sup> The risk of developing metastatic disease ranges from 0.0028 to 0.55 percent.<sup>1</sup> The time from initial tumor to metastases is about 9 years, the survival of which ranges from 8 months to 3.6 years.<sup>1</sup> Sites of metastatic disease include the regional lymph nodes, bone, lung, and liver. Several factors increase the risk of subclinical extension and subsequent recurrent and/or metastatic disease: initial tumor size over two centimeters, lesions originating on the central part of the face or ears, long duration of original lesion, incomplete excision, an aggressive histological growth pattern, or involvement of the perineural or perivascular areas.<sup>1</sup> Tumors with indistinct borders and extension from the original lesion are more often associated with positive margins after excision. These tumors also have a higher recurrence rate compared to well-defined and limited tumors.<sup>3</sup> The low prevalence of advanced disease is due to several reasons such as the indolent nature of the disease, the early detection of small, visible lesions on the skin, and the high cure rate of surgical resection.<sup>3</sup> However, in rare instances, this disease is incurable when the tumors become unresectable and metastasize. The new class of targeted agents, Hedgehog (Hh) antagonists, which inhibit the driving force of BCC pathogenesis, offers optimism in an arena where no other proven standard treatment is available.

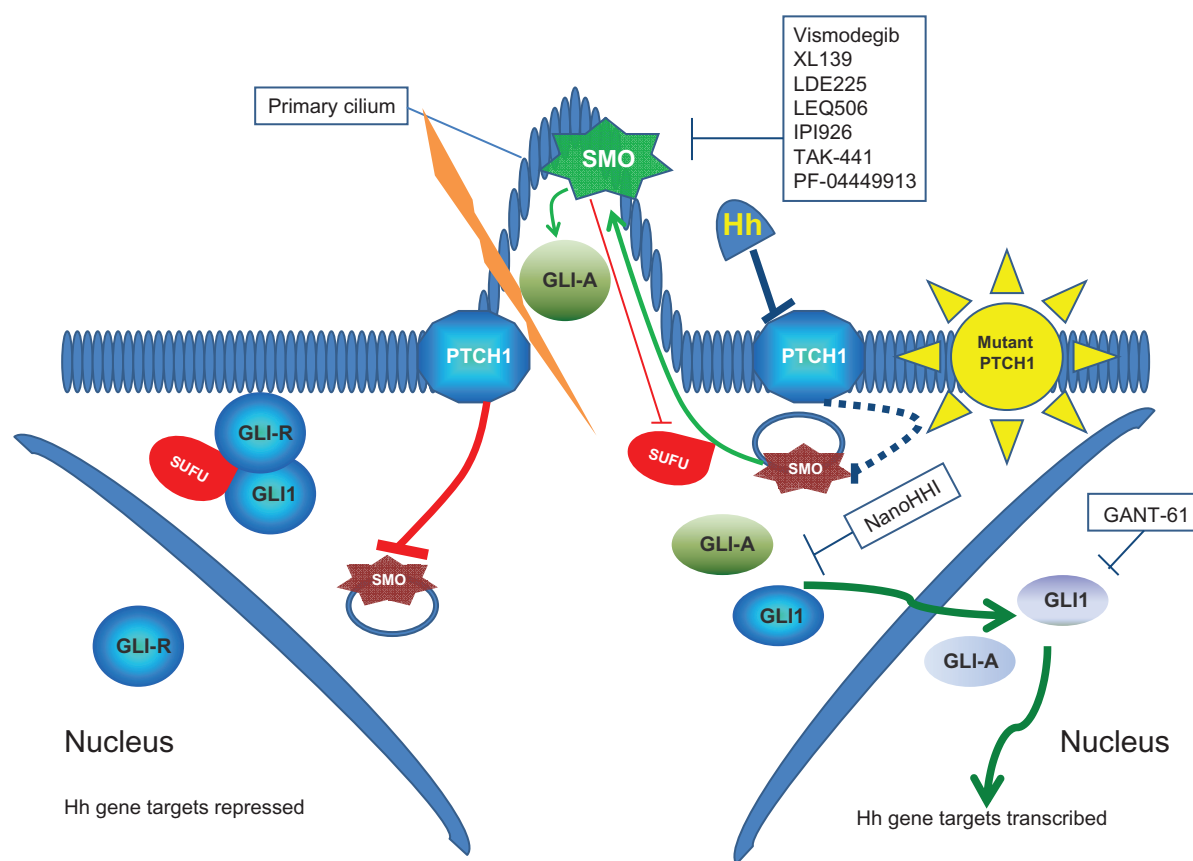
## The role of the hedgehog pathway

In 1980, while they were examining mutations that may disrupt the growth of the fruit fly *Drosophila*, Christiane Nusslein-Volhard and Eric F. Weischaus discovered

Correspondence: Grace K Dy  
Roswell Park Cancer Center  
Elm and Carlton St, Buffalo NY, USA  
Tel +1 (716) 845-3099  
Fax +1 (716) 845-8935  
Email [grace.dy@roswellpark.org](mailto:grace.dy@roswellpark.org)

the Hedgehog gene.<sup>4</sup> This gene was named after the “spiked” phenotype of the cuticle of the Hedgehog mutant larvae of *Drosophila*.<sup>5</sup> The Hedgehog family of proteins was shown later to play a vital role in vertebrate embryonic development. There are three Hh homologs that act as ligands: Sonic Hedgehog (*SHH*), Indian Hedgehog (*IHH*) and Desert Hedgehog (*DHH*).<sup>6</sup> Cell fate control, patterning, proliferation, survival and differentiation were implicated in varying contexts with Hh members. These are essential in the development of the embryonic tissue that controls the movement and organization of cells throughout morphogenesis. This process occurs by forming a concentration gradient or by acting as mitogens. The latter are involved in the regulation of cell proliferation and shaping developing organs.<sup>6</sup> The Hh signaling pathway can be dysregulated by either ligand-dependent or ligand-

independent mechanisms for which there are at least three basic models proposed to underscore the molecular events involved.<sup>7</sup> The type I model refers to ligand-independent constitutive activation of Hh pathway arising from mutations that either inactivate the negative regulators (eg, mutations in *PTCH1* or *SUFU*) or activate the receptor smoothed homolog (mutations in *SMO*) and/or its downstream mediators such as via amplification of the *GLI1* transcription factor (Figure 1). Type II model refers to ligand-dependent pathway activation via autocrine loop signals, such as secretion of Hh ligands that binds to *PTCH1* on cancer cells. Ligand-dependent paracrine signaling classically refers to the Type III model wherein there is activation of stromal cells by Hh ligands secreted by tumor cells, which in turn receives other growth signals from the stroma. A newer variation, called



**Figure 1** Hedgehog (Hh) signaling.

**Notes:** Normal activation of the signaling pathway results from the binding of Hh ligand to the 12-transmembrane patched 1 (PTCH1). As represented in the left half of the figure (demarcated by the jagged orange line), the absence of the Hh ligand allows PTCH1 to repress the activity of the seven-transmembrane G protein coupled receptor-like receptor smoothed homolog (SMO) which is located in intracellular endosomes. Under this state, the GLI transcription factors GLI2 and GLI3 form a complex with the regulatory suppressor of fused (SUFU) protein, which is then either degraded by the proteasome or processed into repressor forms that cannot activate target gene transcription.<sup>42</sup> SUFU also acts to sequester GLI1, which is constitutively active and does not contain repressor domain.<sup>43</sup> When Hh ligand is available as represented in the right half of the figure, PTCH1 exits out of the primary cilium and permits SMO to translocate to the plasma membrane, concentrating in the cilia of some cell types. Activated SMO suppresses SUFU function, which renders the GLIs stable and active, such as by reduction of repressor forms. In the nucleus, activated GLI permits the target gene expression, such as *CCND1*, *PTCH1*, and *GLI1*. Type I Hh signaling is ligand-independent aberrant activation, such as by functional inactivation of PTCH1 through mutations resulting in constitutive activation of SMO and downstream GLI-mediated transcription of genes. Drugs inhibiting SMO are shown in the text boxes.

**Abbreviations:** GLI-R, GLI2 and GLI3 repressor forms; GLI-A, GLI2 and GLI3 transcriptional activators; Hh, Hedgehog; NanoHhI, polymeric nanoparticle formulation of Hh pathway inhibitor-I; PTCH1, patched 1; SMO, smoothed; SUFU, suppressor of fused.

type IIIb, is a reverse paracrine signaling whereby Hh ligands secreted by cells in the stroma leads to Hh pathway activation in the cancer cell (reviewed in detail by Scales et al<sup>8</sup>). Moreover, evidence is emerging supporting the role of Hh pathway in mediating treatment resistance and disease relapse through the maintenance of putative cancer stem cells in the microenvironment.<sup>7</sup>

The type I aberrant Hh signaling has been identified as the key molecular event implicated in BCC tumorigenesis.<sup>5,6</sup> The tumorigenic potential of deregulated Hh signaling was first identified in BCC. Family-based linkage studies of patients with Gorlin's syndrome have led to the discovery of the causative mutation. It was mapped to the Patched 1 gene (*PTCH1*) on chromosome 9.<sup>9</sup> Loss of *PTCH1* predisposes patients with Gorlin's syndrome to develop BCC. In 90% of sporadic form of BCC, at least one allele of *PTCH1* is the identifiable mutation and the remainder of 10% has activating mutations in the *SMO* (gain of function) that reduces inhibition by *PTCH1*. Unrestrained constitutive signaling of the Hh pathway causes proliferation of basal cells in mouse models of BCC.<sup>10</sup> As type I mechanism is ligand-independent, inhibition of the ligand-*PTCH1* interface, such as the use of monoclonal antibodies or trap agents will not be effective.

## Overview of current therapeutic strategies

The therapeutic modalities for patients with advanced/inoperable BCC are limited. Traditionally, systemic chemotherapy has been utilized in this setting and allogeneic organ transplantation in specific cases. The level of supporting evidence is weak as it is based on case reports; the lack of randomized controlled clinical trials is due to the low prevalence of metastatic BCC. A review of the literature revealed that cisplatin-based regimens are relatively effective in treating this disease. This is based on several case reports.<sup>11,12</sup> Nonetheless, the NCCN guideline continues not to recommend a specific chemotherapy regimen in this setting.

## Vismodegib

Vismodegib is a small molecule inhibitor of the receptor SMO.<sup>13,14</sup> It was approved by the United States Food and Drug Administration (FDA) on January 30, 2012 for the treatment of adults with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma which recurred following surgery or who are not candidates for surgery/radiation based on efficacy results in 104 patients demonstrated in a single-arm parallel cohort trial.<sup>15</sup> In this nonrandomized trial examining 33 patients with metastatic BCC and 71 cases

ineligible for surgery and/or radiation therapy, the median duration of response was 7.6 months and the overall response rates by independent review were 30% and 43% in patients with metastatic and locally advanced BCC, respectively. Patients were shown to be able to remain on the treatment for approximately a year with acceptable toxicities.<sup>15</sup>

## Pharmacokinetics/pharmacodynamics

Following a single oral fasting dose of vismodegib in a phase I study in cancer patients, the maximum total or unbound plasma concentrations were achieved by the second day, with sustained plasma level concentration observed throughout the 6-day washout period.<sup>16</sup> Interestingly, with multiple dosing, steady-state concentrations (C<sub>ss</sub>) were achieved earlier than expected (estimated half-life is approximately 10–14 days following a single 150-mg oral dose in healthy volunteers),<sup>17</sup> ie, within 7–14 days.<sup>16</sup> Unbound drug constituted less than 1% of total drug concentrations regardless of dose or total plasma concentration.<sup>16</sup> Moreover, with multiple daily dosing, there was lack of dose-proportionality in the C<sub>ss</sub>, ie, average C<sub>ss</sub> was similar across different dose cohorts (150 mg, 270 mg, 540 mg), suggesting nonlinear pharmacokinetics.<sup>16</sup> Pharmacodynamic evaluation of post-treatment normal skin biopsy showed downregulation of *GLII* mRNA expression in approximately 75% of patients compared with pretreatment specimens, without correlation between the magnitude of *GLII* downregulation and dose cohort.<sup>14</sup> The recommended phase II dose was thus established at the lowest dose cohort of 150 mg/day since higher doses did not result in increased steady state plasma drug concentration and no dose-limiting toxicities were observed.<sup>14</sup>

PK modeling suggested that saturable, solubility-limited absorption could explain the nonlinearity in terms of dose, and slow clearance for the sustained concentrations, whereas high protein-binding component can explain the small volume of distribution and the low, unbound fraction.<sup>16</sup> Indeed, vismodegib levels were strongly correlated with alpha 1-acid glycoprotein (AAG) levels which it binds with high affinity (K<sub>d</sub> = 13 uM).<sup>18</sup> Nonetheless, due to the relative abundant concentration compared to AAG, human serum albumin represents a high-capacity drug-binding protein albeit of lower affinity relative to AAG (K<sub>d</sub> = 120 uM).<sup>18</sup>

Due to the nonlinearity as described above, a PK-dose scheduling study was conducted to evaluate whether less frequent dosing can result in similar steady-state levels achieved through daily drug administration.<sup>19</sup> This study randomized patients to either daily dosing, three-times-a-week (TIW) or once weekly (QW) schedule after an initial loading

phase of daily 150 mg for 11 days. Patients were stratified according to baseline AAG concentration. By day 29 (after two weeks of alternative dosing schedule), total C<sub>ss</sub> was reduced in a less than dose-proportional fashion, with the lowest level in the once-weekly group. Moreover, the reduction in unbound concentration was even more pronounced than the total drug concentrations at a dose-proportional fashion suggesting linear PK of unbound vismodegib. By the 6th week of the alternative dosing schedules, the total and unbound vismodegib C<sub>ss</sub> had declined by an average of 24% and 46% for the TIW group, and by 50% and 80% for the QW group respectively, relative to the initial levels after the loading phase. Only the standard daily dosing regimen provided unbound vismodegib C<sub>ss</sub> in excess of the target IC<sub>95</sub> value range of 42 to 68 nmol/L for GLI1 inhibition.<sup>20</sup> Whereas the mean unbound C<sub>ss</sub> in the TIW group was greater than the target IC<sub>95</sub> values, almost half of the patients in this group had concentrations below the more conservative target level of 68 nmol/L. For the QW group, majority of patients had unbound C<sub>ss</sub> below the IC<sub>95</sub> target. The aforementioned PK modeling developed during the previous phase I studies in fact prospectively predicted the actual PK results eventually observed from this current study. This mechanistic PK model was then extended to explore the effect of using a lower once daily dose on the total and unbound C<sub>ss</sub>, which verified that the optimal dosing is indeed 150 mg once daily.<sup>19</sup>

Healthy volunteer studies of vismodegib showed that nearly all of the total circulating drug-related components are the parent drug (>98%).<sup>21</sup> The metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage. It is eliminated by a combination of slow elimination, extensive metabolism and excretion of parent drug, the majority of which is excreted through the fecal route. Only a minor amount of an administered dose is recovered in urine.<sup>21</sup>

### Safety and tolerability

Due to the known embryotoxic potential of the pathway, stringent pregnancy precautions were used during clinical trials. Vismodegib may not be a therapeutic option for younger patients either as it may interfere with developing teeth and bones.<sup>22</sup> The most common toxicities observed in the conducted trials to date were primarily constitutional symptoms such as fatigue, gastrointestinal, and musculoskeletal manifestations. Overall, most reported adverse events were of mild to moderate (Common Toxicity Criteria grades 1 and 2) severity,<sup>13,14</sup> of which muscle spasms and dysgeusia were the most common. Other low-grade toxicities including nausea and vomiting, dyspepsia, alopecia and weight loss were observed. On the other hand, a few grade 3 and 4 toxicities were seen, consisting of weight loss and fatigue in less than 10% of the examined cases.<sup>13,14</sup> Fatigue, hyponatremia, muscle spasms, abdominal pain and atrial fibrillation were other rare Grade 3 adverse events.<sup>13,14</sup> Some of these side effects are not unexpected due to the

**Table 1** Other Hh pathway antagonists<sup>41</sup>

Agent	Solid tumors <sup>a</sup>	Hematologic malignancies <sup>b</sup>	Phase <sup>c</sup>	FDA <sup>d</sup>	Company <sup>e</sup>
XLI39 (BMS 833923)	Inoperable, metastatic gastric, gastroesophageal, or esophageal adenocarcinomas, Advanced solid tumors, non-small cell lung cancer	Chronic phase CML Multiple myeloma	I/II	No	Bristol Myer Squibb
LDE225	Skin BCC in Gorlin syndrome, Locally advanced or metastatic pancreatic cancer	Resistant CML	I	No	Novartis
LEQ506	Advanced solid tumors	None	I	No	Novartis
IPI926	Advanced pancreatic adenocarcinoma, recurrent head and neck cancer, metastatic or locally advanced chondrosarcoma	Myelofibrosis	Pilot/I/II	No	Infinity
TAK-441	Advanced BCC	None	I	No	Millennium
PF-5274857	Medulloblastoma		Preclinical	No	Pfizer
PF-04449913	Advanced/metastatic solid tumor	Refractory hematologic malignancies, AML, high risk MDS <sup>6</sup>	I	No	Pfizer

**Notes:** <sup>a</sup>Type of solid tumors currently tested; <sup>b</sup>type of hematological malignancies currently tested; <sup>c</sup>type of active clinical trials; <sup>d</sup>FDA: approval; <sup>e</sup>pharmaceutical company.  
**Abbreviations:** CML, chronic myeloid leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

**Table 2** Clinical trials of vismodegib, as a single agent or in combination with chemotherapies and/or targeted therapies<sup>41</sup>

NCT	Regimen	Target population	Status	Phase
NCT01537107	Sirolimus and Vismodegib	Inoperable solid tumors or pancreatic cancer	Recruiting	I
NCT01543581	Vismodegib	BCC	Not recruiting yet	II
NCT01367665	Vismodegib	Locally advanced or metastatic BCC	Recruiting	II
NCT01330173	Vismodegib	High-risk first remission or relapsed multiple myeloma who received an autologous stem cell transplant	Recruiting	I
NCT01546519	Vismodegib	Advanced solid malignancies including hepatocellular carcinoma	Not recruiting yet	I
NCT00878163	Erlotinib and vismodegib with or without gemcitabine	Metastatic pancreatic cancer or inoperable solid tumors	Unknown	I
NCT00982592	Fluorouracil, leucovorin calcium, oxaliplatin (FOLFOX) and with either vismodegib or placebo	Advanced stomach cancer or gastroesophageal junction cancer	Recruiting	II (randomized)
NCT01267955	Vismodegib	Advanced chondrosarcomas	Recruiting	II
NCT01064622	Gemcitabine with or without vismodegib	Recurrent or metastatic pancreatic cancer	Recruiting	II (randomized)
NCT01163084	Leuprolide acetate or goserelin with or without vismodegib followed by surgery	Locally advanced prostate cancer	Active, not recruiting	I/II (randomized)
NCT00887159	Cisplatin and etoposide with or without either vismodegib or cixutumumab	Extensive-stage small cell lung cancer	Recruiting	II (randomized)
NCT01154452	RO4929097 with or without vismodegib	Advanced or metastatic sarcoma	Recruiting	Ib/II (randomized)
NCT01239316	Vismodegib	Pediatric patients with recurrent or refractory medulloblastoma	Recruiting	II
NCT01088815	Vismodegib	Metastatic adenocarcinoma of the pancreas	Recruiting	II
NCT01096732	Vismodegib	Pancreatic ductal adenocarcinoma in the preoperative setting	Recruiting	II
NCT00939484	Vismodegib	Adult patients with recurrent or refractory medulloblastoma	Recruiting	II
NCT01195415	Gemcitabine and vismodegib	Advanced pancreas cancer	Recruiting	Pilot
NCT01201915	Vismodegib	Operable BCC	Recruiting	II
NCT01239316	Vismodegib	Recurrent or refractory medulloblastoma	Recruiting	II
NCT01556009	Vismodegib versus photodynamic therapy	Multiple BCCs (eg, Gorlin syndrome)	Not recruiting yet	II (randomized)

on-target effects of Hh pathway in taste bud papillae formation and hair follicle growth.<sup>23,24</sup>

### Mechanisms of resistance to vismodegib

In the seminal clinical trial of vismodegib, there was dramatic tumor shrinkage in a patient with metastatic medulloblastoma.<sup>14,25</sup> Molecular profiling showed that the patient's primary and metastatic tumors prior to vismodegib therapy harbored an inactivating somatic *PTCH1* mutation, thus resulting in lack of SMO repression.<sup>26</sup> Upon disease progression, molecular profiling and re-biopsy of a progressing lesion were performed by the Genentech team led by De Sauvage.<sup>26</sup> Aside from the previously detected *PTCH1* mutation, a new G-to-C missense mutation at

position 1697 of SMO was identified, which changed the amino acid from Asp to His in codon 473.<sup>26</sup> In functional studies performed, SMO-D473H per se does not have oncogenic properties in the presence of wildtype *PTCH1*. This acquired resistance mutation resulted in a loss of physical interaction between vismodegib and SMO, thereby impairing drug binding to its target.<sup>26</sup> In fact, substitution of D473 with every other amino acid conferred functional resistance to vismodegib, some of which have oncogenic potential.<sup>27</sup> Another prospective site of mutation identified using an alanine scan mutagenesis approach was at E518, which conferred resistance to vismodegib while remaining functionally intact.<sup>27</sup> To overcome these structural limitations, second-generation SMO antagonists, such as

the bis-amide analogs with activity against vismodegib-resistant SMO are in development.<sup>28</sup>

Establishment of drug-resistant tumor cell lines further revealed that other mechanisms of resistance to SMO inhibition maybe mediated downstream of SMO, such as by cyclin D1 (*CCND1*) or *GLI* amplification.<sup>27,29</sup> Moreover, treatment with a PI3K inhibitor greatly reduced tumor growth in both vismodegib-sensitive and -resistant models,<sup>27</sup> suggesting that tumors with acquired resistance remain dependent on PI3K signaling. Indeed, combination of a SMO inhibitor with a PI3K inhibitor may delay the onset of drug resistance in preclinical models.<sup>29</sup>

## Other investigational agents

Multiple other SMO antagonists are under investigation in the clinic. Overall they are orally administered and are being evaluated in variety of malignancies (Table 1). Several of the adverse events associated with vismodegib are also seen with other Hh antagonists in clinical development (muscle spasms, dysgeusia, alopecia).<sup>30–33</sup> These events are likely on-target effects as elucidated earlier. Topical administration of LDE225 has shown promising results in a small study among patients with nodular and superficial BCC with tumor response correlating with a decrease in Hh target gene expression.<sup>34</sup> More recently, calcitriol has been shown to inhibit Hh signaling and proliferation in BCC independent of its effects on the vitamin D receptor. Its target is likely SMO as SMO-deficient cells were unaffected by calcitriol treatment. However, the exact mechanism of activity is yet unknown.<sup>35</sup>

Distinct from SMO antagonists that can overcome resistance to vismodegib mediated by *SMO* mutations are compounds that target *GLI*. There are multiple steps in *GLI* regulation that can be pharmacologically modified.<sup>36</sup> GANT61 is a small molecule that inhibits *GLI1*-mediated transcription by interfering with DNA binding.<sup>37</sup> NanoHhI is a polymeric nanoparticle formulation of HPI-1, a *GLI1* antagonist that disrupts *GLI* activation and increases *GLI* repressor forms.<sup>36,38</sup> NanoHhI can inhibit Hh signaling in cells with ectopic expression of the *SMO* D473H mutation.<sup>38</sup> Naturally occurring inhibitors of *GLI*-mediated transcription identified from cell-based assay screening include zerumbone, staurosporinone, arcyriaflavin and physalins.<sup>39</sup>

## Conclusions and future directions

Vismodegib is a novel first-in-human, first-in class, orally bioavailable Hedgehog pathway signaling inhibitor of SMO, which was approved in the United States. Numerous clinical

trials are recruiting patients to explore the role of vismodegib as monotherapy or in combination with chemotherapies and/or targeted therapies, not only in BCC but in other malignancies as well (Table 2). Successful clinical development of second-generation agents as well as combinatorial approaches with other targeted therapies may help to circumvent the emerging mechanisms of resistance in this setting. Furthermore, research is ongoing to elucidate biomarkers of treatment response and resistance. Enhanced understanding of the function of the primary cilium, a subcellular organelle protruding from the plasma membrane, has revealed its dynamic role in facilitating the transport and interactions of Hh pathway proteins. It has thus been recently suggested that absence of primary cilia in cancer cells may predict lack of efficacy of SMO inhibitors and may explain the lack of response to vismodegib in BCC with *PTCH1* or *SMO* mutations.<sup>40</sup> This warrants further investigation in prospective studies. Availability of pre- and post-treatment biopsies will facilitate these biomarker and mechanistic studies, which should evaluate both the cancer cell and surrounding stroma as well.

## Disclosure

The authors report no conflicts of interest in this work.

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