Advanced basal cell carcinoma, the hedgehog pathway, and treatment options – role of smoothened inhibitors

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Abstract: Cutaneous basal cell carcinoma (BCC) is the most common human cancer and its incidence is rising worldwide. Ultraviolet radiation exposure, including tanning bed use, as well as host factors play a role in its development. The majority of cases are treated and cured with local therapies including surgery. Yet, the health care costs of diagnosis and treatment of BCCs in the US is substantial. In the United States, the cost of nonmelanoma skin cancer care in the Medicare population is estimated to be US$426 million per year. While rare, locally advanced BCCs that can no longer be controlled with surgery and/or radiation, and metastatic BCCs do occur and can be associated with significant morbidity and mortality. Vismodegib (GDC-0449), a smoothened inhibitor targeted at the hedgehog pathway, is the first US Food and Drug Association (FDA)-approved agent in the treatment of locally advanced, unresectable, and metastatic BCCs. This class of agents appears to be changing the survival rates in advanced BCC patients, but appropriate patient selection and monitoring are important. Multidisciplinary assessments are essential for the optimal care and management of these patients. For some patients with locally advanced BCC, treatment with a hedgehog inhibitor may eliminate the need for an excessively disfiguring or morbid surgery.

Keywords: basal cell carcinoma, hedgehog, smoothened, vismodegib, Gorlin, basal cell nevus syndrome

Introduction
Cutaneous basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) comprise the majority of nonmelanoma skin cancers with an estimated annual incidence between two and three million in the US.1 Approximately 80% of nonmelanoma skin cancers are BCCs, making it not only the most common skin cancer but also the most common cancer in general. The incidence of BCCs continues to rise throughout the world. However, due to treatment in a variety of clinical settings and lack of a registry, the actual incidence of BCC can only be estimated.2 Localized BCCs are typically managed by dermatologists and surgeons with local therapies such as electrodessication and curettage, intralesional injections, topical therapies including imiquimod and 5-fluorouracil, photodynamic therapy, Mohs micrographic surgery, and surgery.3 Radiation is another modality that can be used in the definitive treatment of BCCs in certain cases.4

BCC, nevoid basal cell carcinoma syndrome (NBCCS), and the hedgehog pathway
BCC correlates, as do other skin cancers, with ultraviolet (UV) radiation exposure.5 However, intense intermittent exposure and exposure early in life may play a greater
role in initiation of BCC as opposed to the role of chronic UV exposure in cutaneous SCC. This pattern of UV exposure correlates with the most common anatomic site for BCC, the head and neck. Further, the impact of tanning bed use on the incidence of BCC has also been clearly established, where the risk is greater for the young. Exposure to ionizing radiation also plays a role in later development of BCC. Other risk factors include host factors such as eye and hair color, skin tone, immunosuppressed states seen in conditions such as HIV positivity and organ transplantation, as well as genetic syndromes such as NBCCS or Gorlin syndrome, xeroderma pigmentosum, and albinism.

NBCCS, also called basal cell nevus syndrome or Gorlin syndrome, is a rare autosomal dominant disorder that manifests with multiple BCCs at a young age and includes benign tumors, such as jaw keratocysts and meningoimias, and malignant neoplasms, such as medulloblastoma and rhabdomyosarcoma, as well as other defects including bifid ribs and mental retardation. Inactivating mutations of the PTCH1 gene, located on chromosome 9q, were first described in NBCCS and later in sporadic BCCs. The PTCH1 gene, a member of the sonic hedgehog pathway (SHH), encodes a transmembrane protein that binds and inhibits another transmembrane protein and activator, smoothened (SMO), thus inactivating SHH pathway signaling. The SHH pathway is critical during embryonic development due to involvement in cellular proliferation. However, when activation of SHH pathway occurs, proliferation and cell growth is supported via the transcription of several downstream genes, including GLI1–3. The SHH pathway also has extensive interactions with other pathways, including the MAPK and PI3K pathways. Interestingly, a variety of germline and somatic mutations are present in PTCH1 in BCCs and other tumors from NBCCS patients; somatic PTCH1 mutations, as well as rare SMO mutations, have been described in sporadic BCCs. Further, p53 mutations are found in sporadic and inherited BCCs and can be accompanied by PTCH1 alterations. Not surprisingly, the incidence of typical UV-associated PTCH1 mutations is greater in patients with xeroderma pigmentosum than in those with sporadic BCCs. Cyclopamine is a naturally occurring inhibitor of SMO that was discovered in the California corn lily due to its teratogenic effects on the lambs born from the mothers who ate the lilies. Vismodegib (GDC-0449; Genentech-Roche, South San Francisco, CA, USA), an orally bioavailable SMO inhibitor, was designed and selected for further clinical development.

BCC contributes little to cancer-related mortality, but due to very high incidence it does carry significant costs in terms of morbidity, quality of life, as well as direct and indirect financial costs. Modifying personal risk factors including sun/UV protection and avoidance and tanning bed avoidance could have significant impact on wellness as well as health care spending. Regular monitoring of patients with unmodifiable risk factors, such as immunosuppression, is also critical. These societal and cultural norms are addressed in the US Surgeon General’s recent Call to Action regarding skin cancer. This important initiative strives to educate people regarding safe UV practices and improve access to UV protection, improve awareness and understanding of all skin cancers, as well as support continued research in the field. A similar sentiment regarding sun protection and skin cancer awareness is included as one of the codes in the European Cancer League’s 2014 Code against Cancer.

Advanced BCC

Advanced BCC, or “advanced stage” BCC, is divided into two categories: locally advanced tumors (laBCCs) and metastatic disease (mBCC). “Typical” slow-growing BCC is rarely staged as most are small primaries confined to the skin. LaBCC includes primary tumors that invade and extend beyond the skin, including cartilage, muscles, bone, or have metastatic spread to skin and/or lymph nodes that do not spread beyond the immediate vicinity of the primary site. LaBCCs pose quite a challenge to management as the definition of “surgically resectable” carcinoma is challenging and variable. While some are clearly unresectable, others may be resectable, but the patient remains at extremely high risk of recurrence. The most difficult cases are those that may be technically resectable, but the procedure results in functional impairments or excessive morbidity. It is often challenging to determine when surgery can and should be pursued. Metastatic BCC is defined as distant spread to another organ or nonregional lymph node or skin involvement, as are other metastatic solid tumors. Identifying patients at risk for advanced BCC remains a challenge and research into determinants of “aggressive behavior” continues. Some patients may present with fairly slow-growing, or typical, BCCs that recur locally and ultimately become unresectable (laBCC) or develop metastases. Pathologically, “aggressive behavior” in BCCs appears to correlate with the depth of invasion, perineural invasion, vascular invasion, ulceration/erosion, and sclerosis. In a retrospective single-center analysis, the “moderate and severe” cases of BCC were significantly associated with a “unique” histologic...
diagnosis and had a higher association with basosquamous carcinoma and sclerosing BCC. Clinically, depth and diameter of the primary lesion, anatomic location, close or positive margins at the time of excision, as well as recurrence after surgery or radiation all increase the risk of developing advanced BCC. A higher risk for recurrence and/or advanced disease in immunosuppressed patients has also been suggested. Interestingly, size of the primary BCC at presentation is not always predictive of fatal outcomes but can cause significant morbidity. Very large lesions can be associated with a delay or late presentation for medical attention due to neglect, psychiatric or other comorbidities, lack of access to medical care, or limited finances.

The incidence of mBCC is estimated at 0.0028%–0.5% and is quite rare. As previously stated, BCC can metastasize with the most common sites being skin, lymph nodes, lungs, and bone with a median time to metastatic relapse of approximately 9 years. Standard imaging procedures including computed tomography (CT), magnetic resonance imaging (MRI), and PET (positron emission tomography) CT should be pursued as well as biopsy of the distant site to establish the diagnosis and stage of the disease according to the updated nonmelanoma skin cancer staging system.

Survival for locally advanced disease that is resectable is typically better than the reported median overall survival (OS) for locally advanced, unresectable, or metastatic BCC of less than 1 year in historic and contemporary reviews. However, overall survival in mBCC appears improved compared to historical reports. One recent review of ten patients with mBCC treated at a single center from 1997 to 2011 reported a median OS of 7.3 years. In this report, nine of the ten patients received systemic therapies including chemotherapy (n=3) and SMO inhibitors (n=6), and all the patients who had received SMO inhibitors and one of the chemotherapy patients were still alive (0.6–7.8 years from diagnosis). Additional contemporary survival data has come from patients treated with vismodegib in clinical trials which reported a notable 1-year OS of 84.4% and a median OS of 2.8 years.

**Treatment**

**Definitive therapy**

Surgical excision is still the gold standard treatment for early stage, localized BCC. This may involve simple excision versus the use of Mohs micrographic technique. Depending upon the part of the body involved, multiple subspecialists may be needed and may involve reconstruction in order to achieve clear surgical margins, preserve adequate functionality, as well as acceptable cosmesis. As laBCC is not a common entity, physicians with experience in the management of these patients and a multidisciplinary approach are essential. Surgery still offers the potential for cure in many cases. However, the definition of resectable versus unresectable in laBCC is often challenging and is dependent upon the expertise of the surgeon and the multidisciplinary team. Neoadjuvant SMO inhibitors may have the potential to reduce the extent of surgery required for laBCC, although this has not yet been demonstrated in a clinical trial. Radiation is also a local treatment for BCC that can be pursued with curative intent if the patient is not deemed a candidate for surgery or other topical interventions. Radiation also can play a role in primary treatment in the adjuvant setting when positive margins persist despite maximal surgical excision.

Radiation is contraindicated in patients with genetic syndromes that predispose to skin cancer, including NBCCS and xeroderma pigmentosum, as well as in patients with connective tissue diseases.

**Palliative therapy**

Surgery and radiation can also play a role in palliation of advanced disease, such as with a primary tumor that is painful or bleeding or with painful metastatic sites. Until recently, systemic therapy for advanced BCC was quite limited. However, the advent of hedgehog pathway inhibitors has dramatically expanded the field of systemic treatment of BCC and appears to be impacting survival rates. Prior to recently published SMO inhibitor trials, the primary agent explored in the treatment of advanced BCC was cisplatin, alone and in combination with other chemotherapeutic agents. The first data came from a small Phase I/II study of single-agent cisplatin where one complete response (CR) and one partial response (PR) were seen in two patients with advanced BCC.

Further data included two CRs to single-agent cisplatin in another report, including response upon retreatment. Several small series or case reports demonstrated both PRs and CRs with cisplatin in combination with cyclophosphamide, vinblastine, or doxorubicin as well as cisplatin or carboplatin in combination with paclitaxel. Two reviews compiled the published data from a total of 53 cases of advanced BCC treated with cytotoxic chemotherapy including cisplatin or cisplatin-containing regimens (doxorubicin, 5-fluourouracil, etoposide, methotrexate, cyclophosphamide, bleomycin, and Vinca alkaloids). A cumulative response rate (CR + PR) of 77% (17/22) with a CR rate of 45% and median survival of 22 months was reported by one group; the other group reported a response rate (RR) of 83% (n=46)
with a CR rate of 37% and a PR rate of 46% and a median time to progression of 24 months.

**Vismodegib**

Vismodegib (GDC-0449), the first-in-class SMO inhibitor, was investigated and approved by the US Food and Drug Association (FDA) for the treatment of locally advanced, unresectable BCC and mBCC in 2012. Preclinical data supported activity in medulloblastoma allografts. The first Phase I dose-escalation and dose-expansion study (Table 1) in humans treated 68 patients with advanced malignancies and 33 with advanced BCC. The 33 patients included 18 with mBCC and 15 with laBCC with most treated at 150 mg daily, which was determined to be the recommended Phase II dose. No dose limiting toxicities were seen, however common toxicities included muscle spasms, dysgeusia, fatigue, alopecia, and nausea. There were a few grade 3 events, which included abdominal pain, dyspnea, weight loss, dehydration, and prolonged QTc. Grade 4 events included fatigue, presyncope, hyperglycemia with paranoia, asymptomatic hyponatremia, and pylonephritis. Not all of these grade 3 and 4 toxicities were definitely related to the vismodegib treatment. Clinical activity was determined according to physical exams with or without Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, depending upon whether the sites of disease were radiologically evaluable, where a reduction in visible tumor diameter of >50% was needed to qualify as a PR in laBCC. Patients with mBCC showed an RR of 50% (95% confidence interval [CI]: 29–71); laBCC had an RR of 60% (95% CI: 33–83). Two of the patients with laBCC had a CR. For the entire BCC cohort, the RR was 58% (19/33) and an additional ten patients had stable disease (SD). A complementary pharmacokinetic study did not recommend less frequent than daily dosing despite a long single dose half-life and nonlinear pharmacokinetics. Downmodulation of GLI1 expression was seen in pharmacodynamic studies. Tumor samples were available from ten patients: PTCH1 mutations were identified in nine, including one patient who also had an SMO mutation. Two patients with NBCCs had PTCH1 mutations in normal skin.

ERIVANCE (Efficacy and Safety of the Hedgehog Pathway Inhibitor Vismodegib in Patients With Advanced Basal Cell Carcinoma) is the follow-up multicenter, Phase II study that evaluated the independently-assessed RR to treatment with vismodegib in two cohorts, unresectable laBCC and mBCC. All patients received vismodegib at 150 mg daily. Responses in mBCC were assessed by RECIST 1.0 criteria. For patients with laBCC, response was defined as a 30% decrease in the externally visible dimension or complete resolution of ulceration. Of the 104 patients enrolled and treated, 96 were eligible for analysis with 63 laBCC and 33 mBCC patients. RRs were lower than those in the Phase I study, with 30% (95% CI: 16–48, P=0.001) in the mBCC cohort and 43% (95% CI: 31–56, P<0.001) in the laBCC cohort by independent review. Importantly, there were 13 CRs (21%) in the laBCC cohort, defined as absence of residual BCC on biopsy. The median duration of response (DOR) was 7.6 months for both cohorts and the median progression free survival was 9.5 months. By investigator review, the RRs were 45% (mBCC) and 60% (laBCC) and showed median DOR of 12.9 months and 7.6 months, respectively. There was a minimum disease progression on treatment, as 64% of mBCC and 38% of laBCC patients evidenced SD. The median exposure to study drug was 10 months with 12% discontinuation rate due to adverse events (AEs). Based on the pharmacokinetic profile, dose interruptions of up to 4 weeks were permitted but not dose reductions. The most common toxicities were muscle spasms (68%), alopecia (63%), dysgeusia (51%), weight loss (46%), fatigue (36%), nausea (29%), anorexia (23%), and diarrhea (22%). The frequency of alopecia and dysgeusia can both be explained by the presence of an active hedgehog pathway in the adult hair follicles and taste buds that is inactivated by the SMO inhibitor. The majority of AEs were grade 1; serious AEs occurred in 25% of patients. Seven deaths were reported, including hypovolemic shock, myocardial infarction, stroke, and meningeal disease as well as three patients who died of unknown causes. All of these deaths were reported as unrelated to the study drug, and the patients were noted to have comorbidities or risk factors at baseline.

Based on this Phase II study, vismodegib received FDA approval for the treatment of locally advanced, unresectable BCC and mBCC in January 2012. The results of the ERIVANCE study were updated at 30 months after primary analysis and had comparable investigator-assessed RRs of 48.5% (mBCC) and 60.3% (laBCC). For the mBCC cohort, the median DOR was 14.8 months with a median OS of 33.4 months (18.1-not estimable). In the laBCC cohort median OS was not reached and the median DOR was 26.2 months. Safety data reported a total of 22.1% of patients that discontinued treatment due to AEs; seventeen deaths were reported with none related to treatment. Interestingly, data from a few patients showed persistence of disease control after vismodegib discontinuation and clinical benefit on retreatment in two patients. Additional safety and efficacy data for vismodegib has come from the
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<tr>
<th>Trial phase</th>
<th>Drug</th>
<th>Drug dose</th>
<th>Primary endpoint/ clinical intent</th>
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<th>BCC status/ stage</th>
<th>BCC tumor shrinkage/ response</th>
<th>Median duration of response</th>
<th>Median PFS/ Median OS</th>
<th>Discontinued for AEs</th>
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<tr>
<td>i72,73</td>
<td>Vismodegib (GDC-0449)</td>
<td>Dose escalation/ expansion: 150–540 mg/D</td>
<td>Safety and PK/PD/ palliation</td>
<td>68 BCC cohort: 33</td>
<td>Unresectable laBCC (n=15), mBCC (n=18)</td>
<td>Total BCC RR: 58% (19/33) SD: 33%</td>
<td>12.8 mo and ongoing</td>
<td>Not reported</td>
<td>1 withdrawal</td>
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<td>II-ERIVANCE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Vismodegib (GDC-0449)</td>
<td>150 mg/D</td>
<td>Independently assessed RR (iARR)/ palliation</td>
<td>104 (96 eligible for analysis)</td>
<td>Unresectable laBCC (n=63), mBCC (n=33)</td>
<td>IARR:</td>
<td>Independent assess: laBCC: 7.6 mo mBCC: 7.6 mo INV assess: laBCC: 7.6 mo mBCC: 12.9 mo</td>
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<td>Final update at 30 mo&lt;sup&gt;77&lt;/sup&gt;</td>
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<td>EAP&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Vismodegib (GDC-0449)</td>
<td>150 mg/D</td>
<td>Efficacy, safety, and access/ palliation</td>
<td>120</td>
<td>Unresectable laBCC (n=62), mBCC (n=58)</td>
<td>laBCC RR: 46.4% (6 CRs) SD: 48.2% mBCC RR: 30.8% (2 CRs) SD: 51.3%</td>
<td>Not reported</td>
<td>Not reported</td>
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<td>Global safety study-STEVI&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Vismodegib (GDC-0449)</td>
<td>150 mg/D</td>
<td>Safety/ palliation</td>
<td>300</td>
<td>Unresectable laBCC (n=278), mBCC (n=22)</td>
<td>Third interim analysis (ongoing)- RR: 57.3% (44 CRs) SD: 39%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>35 (1.7%)</td>
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<td>I&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Sonedegib (LDE225)</td>
<td>Dose escalation/ expansion: 100–3,000 mg/D and 250–750 mg bid</td>
<td>Safety and PK-PD/ palliation</td>
<td>103 BCC cohort: 16</td>
<td>Unresectable laBCC, mBCC</td>
<td>BCC RR 37.5% (with 1 CR)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>20 (1.9%)</td>
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<td>Randomized phase II BOLT&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Sonedegib (LDE225)</td>
<td>200 mg daily vs 800 mg daily</td>
<td>RR per central review/ palliation</td>
<td>230</td>
<td>Unresectable laBCC (n=194), mBCC (n=36)</td>
<td>200 mg cohort: laBCC RR: 47% (2 CRs) SD: 44% mBCC RR: 15% SD: 77%</td>
<td>200 mg cohort: laBCC: NE mBCC: NE</td>
<td>200 mg cohort: 800 mg cohort: laBCC: NE mBCC: 8.3 mo mOS not reported</td>
<td>200 mg cohort: 20% 800 mg cohort: 32%</td>
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Table I (Continued)

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<th>Discontinued for AEs</th>
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<tr>
<td>IIT</td>
<td>Saridegib (PI-926)</td>
<td>Dose escalation/expansion: 20–210 mg/D</td>
<td>Safety and P/K-PD/palliation</td>
<td>94</td>
<td>BCC stage: II: 26%</td>
<td>Eleven pts completed tx-27% reduction in surgical defect area from baseline</td>
<td>9 remained on drug, including 2 &gt;700 days</td>
<td>Not reported</td>
<td>6 (6%)</td>
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<td></td>
<td>Vismodegib (GDC-0449)</td>
<td>150 mg/D</td>
<td>Change in target tumor surgical defect area/neoadjuvant</td>
<td>15</td>
<td>At least one operable primary BCC ≥5 mm</td>
<td>Per-patient rate of new surgically resectable BCCs in vismodegib cohort: 2 vs 29 cases per group/yr, and significant reduction in size of existing BCCs (≥5% vs &lt;11%)</td>
<td>Not reported</td>
<td>4/14 unable to complete &gt;3 mo of tx</td>
<td>54% (14/26) on vismodegib</td>
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<td>Randomized</td>
<td>Vismodegib vs placebo (2:1)</td>
<td>150 mg/D</td>
<td>Reduction in incidence of new BCC eligible for surgery/neoadjuvant</td>
<td>41</td>
<td>NBCCs pts with multiple primary BCCs</td>
<td>n/a</td>
<td>n/a</td>
<td>54% (14/26) on vismodegib</td>
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<td>Exploratory</td>
<td>Itraconazole</td>
<td>200 mg vs 100 mg bid and control</td>
<td>Change in Ki-67 and GLI1 mRNA/neoadjuvant</td>
<td>29 enrolled, ≥1 operable BCC &gt;4 mm</td>
<td>4% reduction in Ki-67 and 65% reduction in HH activity; ≥24% reduction in size of tumor</td>
<td>n/a</td>
<td>n/a</td>
<td>11% (2/19)</td>
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Abbreviations: BCC, basal cell carcinoma; PFS, progression free survival; OS, overall survival; AE, adverse event; D, day; mo, month; yr, year; RR, response rate; NR, not reached; bid, twice daily; PK, pharmacokinetics; PD, pharmacodynamics; laBCC, locally advanced BCC; mBCC, metastatic BCC; SD, stable disease; iNv, investigator assessed; CR, complete response; EAP, expanded access program; NM, not mature; NE, not estimable; IIT, investigator initiated trial; n/a, not applicable; iARR, independently assessed response rate; mOS, median overall survival; tx, treatment; pts, patients; NBCCS; nevoid basal cell carcinoma syndrome; HH, hedgehog.

Of note, there are now several reports of SCCs arising from pre-existing keratosis, and possible collision lesions with regression of the BCC and growth of the remaining SCC component. In the absence of new evidence, it is assumed that the full course of circumstances in patients on vismodegib therapy has been described including the nevoid basal cell carcinoma syndrome. The expanded access program was started in 2015, and included 140 patients, with 120 treated with vismodegib. The side effects seen in the Phase II study were similar to those seen in the Phase III study, with an objective RR of 30.8% (95% CI: 17.0–47.6). Of note, there are now several reports of SCCs arising from pre-existing keratosis, and possible collision lesions with regression of the BCC and growth of the remaining SCC component. In the absence of new evidence, it is assumed that the full course of circumstances in patients on vismodegib therapy has been described including the nevoid basal cell carcinoma syndrome. The expanded access program was started in 2015, and included 140 patients, with 120 treated with vismodegib. The side effects seen in the Phase II study were similar to those seen in the Phase III study, with an objective RR of 30.8% (95% CI: 17.0–47.6). The expanded access program was started in 2015, and included 140 patients, with 120 treated with vismodegib. The side effects seen in the Phase II study were similar to those seen in the Phase III study, with an objective RR of 30.8% (95% CI: 17.0–47.6). The expanded access program was started in 2015, and included 140 patients, with 120 treated with vismodegib. The side effects seen in the Phase II study were similar to those seen in the Phase III study, with an objective RR of 30.8% (95% CI: 17.0–47.6). The expanded access program was started in 2015, and included 140 patients, with 120 treated with vismodegib.
Other SMO inhibitors

Several other SMO inhibitors targeting the HH pathway have entered clinical trials. Sonidegib (LDE225) (Novartis, Basel, Switzerland) is a selective SMO inhibitor that recently received FDA approval for the treatment of locally advanced BCC that recurred after surgery or radiation or that cannot be treated with surgery or radiation. A Phase I dose-escalation study of oral sonidegib in advanced solid tumors treated 103 patients, including 16 BCC and nine medulloblastoma patients.87 Two dosing schedules were evaluated and 800 mg once daily and 250 mg twice daily were identified as the maximum tolerated doses. The main dose-limiting toxicity was reversible elevation of creatinine kinase (CK), which did not correlate with muscle spasms. The most common treatment-related AEs were nausea, dysgeusia, anorexia, vomiting, muscle spasms, myalgias, increased CK, fatigue, and alopecia. There were no deaths related to treatment and 19% discontinued treatment due to AEs. GLI1 mRNA expression was evaluated in a small number of samples, which decreased in a dose- and exposure-dependent manner with treatment. Of the BCC patients, 37.5% (6/16) evidenced an objective response including one CR. A randomized Phase II, double-blind study that evaluated the RR to sonidegib at the minimally active biologic dose (200 mg daily) versus the maximum tolerated dose (800 mg daily) was completed in 230 patients with laBCC and mBCC.88 The results demonstrated lower clinical benefit, higher discontinuation rate (69% vs 51%), and lower duration of drug exposure (6.5 months vs 8.9 months) in the higher dose cohort, which can be attributed to poorer tolerability. Rigorous methods of assessing clinical response were used and included both modified RECIST criteria for laBCC and RECIST 1.1 for mBCC patients. Objective RR by central review in the full analysis set for the laBCC cohort was 47% at 200 mg and 35% at 800 mg daily dosing: for the mBCC cohort the RRs were 15% and 17%, respectively.

Saridegib (IPI-926) (Infinity Pharmaceuticals, Cambridge, MA, USA) is another selective small molecule SMO inhibitor that has demonstrated tolerability in a dose-escalation Phase I study in advanced solid tumors.89 This study enrolled 94 patients, including 39 patients with BCC. The recommended Phase II dose was 160 mg daily based on dose limiting toxicities of reversible grade 2/3 aspartate aminotransferase and alanine transaminase elevation. Otherwise, the most common toxicities were fatigue, nausea, alopecia, muscle spasms, anorexia, vomiting, diarrhea, and dysgeusia. Only 6% discontinued the study drug due to AEs and none of the patients died during the study period. Of these patients, 28 were evaluable for response and were naïve to SMO inhibitors. In this group of patients, two CRs and six PRs were seen in laBCC. In the nine patients who had previously received vismodegib, two received IPI-926 therapy for 18 weeks and 50 weeks with no objective responses. Thirteen patients with NCCBS were enrolled and some reported improvement in noncancer-related symptoms of their disease. Development of this drug was discontinued after negative clinical trials were reported for other cancer types.90

Additional agents under clinical investigation include: BMS-833923 (XL139; Bristol-Myers Squibb, New York, NY, USA; Exelexis, South San Francisco, CA, USA), an SMO inhibitor that has demonstrated preliminary efficacy and tolerability, including in one patient with medulloblastoma and another patient with Gorlin syndrome.91 LEQ506 (Novartis, Basel, Switzerland) is a second-generation SMO inhibitor that showed activity in vitro in a resistant SMO D473H mutant cell line similar to TAK-441 (Takeda Pharmaceuticals, Osaka, Japan).92,93 However, TAK-441 development has been discontinued for the treatment of BCC. PF-04449913 (Pfizer, New York, NY, USA) is under investigation for use primarily in hematologic disorders.

Novel and alternative therapeutic strategies with SMO inhibitors

Neoadjuvant/adjuvant therapy

At this time, there is no randomized trial data to support the use of vismodegib in the neoadjuvant or adjuvant setting but data is accumulating. A Phase II, three-cohort study evaluating vismodegib in operable (resectable) BCC followed by Mohs excision completed accrual, but results are not yet available (NCT01201915). Recently, a small investigator-initiated study treated eleven primary BCC patients with vismodegib prior to planned surgery and reported a 27% reduction in the surgical defect area from baseline.94 Several other studies are evaluating neoadjuvant vismodegib in a variety of settings (https://clinicaltrials.gov/ NCT01898598, NCT01543581, NCT01631331). Practically speaking, since very few patients initially progress on an SMO inhibitor, it may be reasonable to consider neoadjuvant therapy in a patient with a locally advanced lesion that is borderline operable.

As primary treatment in NBCCS syndrome/multiple primary BCCs

The role of systemic therapy, including SMO inhibitors, in NBCCS and multiple primary BCCs is not yet established. One Phase II randomized, double-blind, placebo-controlled study in patients with NBCCS evaluated for a reduction in the incidence of new, surgically resectable primary BCCs at
3 months as well as reduction in the size of existing primary BCCs.\(^9\) There was a significant reduction in the per-patient rate of new surgically resectable BCCs in the vismodegib cohort: two versus 29 per year, as well as a significant reduction in the size of existing BCCs in 41 patients. Yet, 54\% of patients discontinued vismodegib due to toxicities, and most patients evidenced BCC regrowth after drug discontinuation. In this study, patients were allowed to remain on study drug for only 18 months. For NBCCS patients, it is not clear from the study at what age and/or phase in their disease should one start vismodegib and for how long should the therapy be continued, questions that are extremely important as the majority of these patients are young.

Several studies are also looking at intermittent therapy in an effort to modulate toxicities and drug exposure. One study seeks to compare intermittent vismodegib dosing versus photodynamic therapy in maintaining benefit following an initial treatment with vismodegib for 7 months in patients who meet criteria for NBCCS with multiple primary BCCs (NCT01556009). Another study is looking at different intermittent regimens of vismodegib therapy over 72 weeks in patients with multiple primary BCCs: one cohort will receive 12 weeks of treatment alternating with 8 weeks of placebo versus 24 weeks of therapy followed by 8 weeks of placebo and then 8 weeks of vismodegib (NCT01815840). Patients with NBCCS are eligible, but this is not required for participation. A small study will assess the incidence of newly diagnosed BCCs over a 24-month period in patients at high risk for BCC (at least three prior occurrences of BCC in the preceding 2 years) and is randomizing patients at high risk for BCC to placebo or vismodegib for 2 months (NCT02067104). Another interesting study is attempting to gauge if the response of vismodegib differs amongst different histologic subtypes of BCC (NCT01700049). Another potential method of minimizing toxicities is alternative routes of delivery, such as topical applications. Sonidegib (LDE225) in a topical form was evaluated in eight NBCCS patients with 27 BCCs in a double-blind, randomized, vehicle-controlled study.\(^9\) Topical treatments were applied to patients with BCCs twice daily for 4 weeks and were well tolerated. Only one PR was seen in the vehicle-treated cohort. In the LDE225 treated group, no complete histologic responses were seen but clinical responses were seen in the 13 treated BCCs (three CR, nine PR), but development of topical Sonidegib has been discontinued.\(^9\) At the moment, whether to initiate vismodegib therapy in Gorlin/NBCCS, and if there is an optimal time to do so, is unknown as are the possible risks and benefits of prolonged use. As with NBCCS, the use and timing of vismodegib in patients with multiple primary BCCs is yet to be determined.

### Rebound and resistance to SMO inhibitors

Data to date support a palliative but not curative role for these agents in the treatment of locally advanced, unresectable, or metastatic BCC. However, the impact of vismodegib on survival should not be minimized. Another important reason for a high degree of patient selection with these agents is the issue of rebound and resistance. While the majority of patients evidence response or SD, there is a small group of patients who show no benefit on treatment for unknown reasons. For those who do respond, toxicities can be an issue and rebound tumor growth after initial response and subsequent cessation of SMO inhibitor treatment has been described in several patients.\(^9\) Information regarding acquired resistance is also accumulating. The first report of acquired resistance occurred in a patient with metastatic medulloblastoma who was treated on the dose-escalation Phase I study with vismodegib at 540 mg daily dosing and manifested a dramatic improvement in tumor size and symptoms.\(^9\) He had a baseline W844C mutation in P\(\text{TCH1}\). Unfortunately, his response was short lived; he progressed for 3 months and was noted to have a new SMO mutation (D473H) that rendered cells insensitive to vismodegib in a mouse model.\(^1\) Tumor resistance to vismodegib subsequently was described in six laBCC patients but no analyses were done.\(^1\) A recent case report described two novel missense SMO mutations in two progressing nodules that regrew in the bed of a laBCC after 5 months of treatment with vismodegib.\(^2\) The authors postulate that additional mutations could also be present, since not all the progressing areas were sequenced. The first report of a mBCC patient that developed resistance was in a man with a long history of advanced BCC with metastases to lymph nodes, lung, and pleura initially treated with surgery.\(^3\) The patient enrolled on a clinical trial with vismodegib 150 mg daily dosing and showed rapid symptom and tumor improvement within 2 months. He manifested a CR but presented after 7 months of treatment with recurrent rib and lung metastases. The patient died 18 months after drug cessation and did not receive other treatments. No molecular or genetic studies were noted in the case report. A recent report enumerates several SMO mutations detected in vismodegib-resistant BCC, many that affected the drug binding pocket.\(^4\) Notably, there was mutational heterogeneity within sampled BCCs supporting complex and distinct resistance mechanisms within individual tumors. Second-generation antagonists remain
under development as discussed earlier. Altered drug binding, amplification of GLI1 and CCND1 and PI3K pathway upregulation have been proposed as possible mechanisms of resistance to SMO inhibitors.\(^{105–107}\) Amplification of GLI1 is under the control of several pathways including RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, EGFR, and Notch.\(^{23}\) Combinatorial drug targeting of the hedgehog pathway plus other pathways may be one approach to overcome resistance.\(^{107}\) Drugs such as the small molecule GANT58 and GANT61 block GLI1 function directly and represent another avenue of overcoming resistance.

Alternative strategies of targeting the HH pathway include agents that inhibit SMO through alternative mechanisms. Itraconazole, an FDA-approved antifungal drug, was identified in a drug screen of FDA-approved agents as an inhibitor of the HH pathway and was postulated to act through prevention of ciliary accumulation of SMO.\(^{108}\) This same group of investigators also identified arsenic trioxide as an inhibitor of HH signaling by inhibiting GLI2 accumulation in cilia and demonstrated that both agents alone and in combination can inhibit growth of SMO wildtype and resistance cells in vitro and in vivo.\(^{109}\) In a small study of 29 patients with primary BCCs, 19 patients received treatment with itraconazole, which showed decreased proliferation and HH pathway signaling and produced a 24% reduction in tumor size.\(^{110}\) There is an ongoing Phase 0 study that is treating primary BCCs with topical itraconazole and will assess for downregulation of GLI1 (NCT02120677). The results of a study treating patients with BCC with arsenic trioxide have not been reported (NCT01791894). Vitamin D3 is endogenously secreted in a PTCH1-dependent manner and acts as an inhibitor of SMO.\(^{111}\) Uhmann et al demonstrated that treatment with calcitriol inhibited BCC growth and proliferation in PTCH1-mutant mice through two mechanisms: SMO inhibition and induction of differentiation via activation of the vitamin D receptor.\(^{112}\) A Phase III study may shed light on the histologic effects of topical calcitriol, diclofenac, or both on primary BCCs (NCT01358045). Finally, another group detected significant increase in expression of ALK oncogene in BCCs compared with normal epidermis as well as increased phospho-ERK on immunohistochemical.\(^{113}\) Exposure to crizotinib, an inhibitor of ALK, significantly reduced expression of GLI1 and CCND2 and thus suggesting a possible role for ALK inhibitor in the treatment of BCCs.

**Conclusion**

Advanced BCC remains a rare entity. The developments in the targeting of the hedgehog pathway are very exciting and the community is seeing clear improvements in the treatment of patients with advanced BCC. However, surgery and other local therapies continue to be the mainstay of treatment. When and at which phase of the disease should the patients undergoing local therapies for laBCC be deferred in favor of systemic therapy remains a difficult decision and should be done on a case-by-case basis. It is possible that neoadjuvant hedgehog inhibitor therapy could allow patients to avoid disfiguring and major surgery, but this has not been clearly established. Trials of neoadjuvant therapy are ongoing for various stages of BCC. Due to the rarity of advanced disease and often challenging circumstances, a multidisciplinary approach including surgeons, dermatologists, radiation and medical oncologists, and others is the key to optimal treatment. The toxicities seen with SMO inhibitors are manageable and carry some predictable class effects. However, they do require monitoring and management including periodic blood work such as kidney and liver function tests, electrolytes and complete blood counts, possible need for nutritional counseling, and strong counseling regarding birth control.\(^{114,115}\) The emergence of rebound and/or resistance is another factor to consider when making treatment decisions. As with all malignancies, research into additional molecular drivers of disease, prognostic and predictive markers, and resistance are imperative and clinical trial participation should be encouraged.

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**References**


