Biologics: Targets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

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

This article was published in the following Dove Press journal:
Biologics: Targets and Therapy
6 November 2015
Number of times this article has been viewed

Leslie A Fecher[1,3]
William H Sharfman[2]

[1]Department of Internal Medicine and Dermatology, Indiana University Health Simon Cancer Center, Indianapolis, IN, USA; [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA, [3]Department of Internal Medicine and Dermatology, University of Michigan, MI, USA

Biologics: Targets and Therapy downloaded from https://www.dovepress.com/
For personal use only.

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

Correspondence: Leslie A Fecher
University of Michigan, C366 MIB,
1500 East Medical Center Drive,
SPC 5848, Ann Arbor, MI 48109-5848 US
Tel +1 734 615 4762
Fax +1 734 936 4940
Email lfecher@med.umich.edu

© 2015 Fecher and Sharfman. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution – Non Commercial (unported, v3.0) License. The full terms of the License are available at http://creativecommons.org/licenses/by-nc/3.0/. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. Permissions beyond the scope of the License are administered by Dove Medical Press Limited. Information on how to request permission may be found at: http://www.dovepress.com/permissions.php

role in initiation of BCC as opposed to the role of chronic UV exposure in cutaneous SCC.[6] This pattern of UV exposure correlates with the most common anatomic site for BCC, the head and neck.[7,8] 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.[9,10] Exposure to ionizing radiation also plays a role in later development of BCC.[11,12] 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.[13–17]

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 meningiomas, and malignant neoplasms, such as medulloblastoma and rhabdomyosarcoma, as well as other defects including bifid ribs and mental retardation.[18,19] Inactivating mutations of the *PTCH1* gene, located on chromosome 9q, were first described in NBCCS and later in sporadic BCCs.[20,21] 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.[22] 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.[23] 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.[24–26] Further, p53 mutations are found in sporadic and inherited BCCs and can be accompanied by *PTCH1* alterations.[27,28] Not surprisingly, the incidence of typical UV-associated *PTCH1* mutations is greater in patients with xeroderma pigmentosum than in those with sporadic BCCs.[29] 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.[30,31] Vismodegib (GDC-0449; Genentech-Roche, South San Francisco, CA, USA), an orally bioavailable SMO inhibitor, was designed and selected for further clinical development.[32]

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.[33,34] 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.[35] Regular monitoring of patients with unmodifiable risk factors, such as immunosuppression, is also critical.[36] These societal and cultural norms are addressed in the US Surgeon General's recent Call to Action regarding skin cancer.[37] 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 Leagues' 2014 Code against Cancer.[38]

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.[39,40] Pathologically, "aggressive behavior" in BCCs appears to correlate with the depth of invasion, perineural invasion, vascular invasion, ulceration/erosion, and sclerosis.[41–43] 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.[8] 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.[7,41,42,44,45] A higher risk for recurrence and/or advanced disease in immunosuppressed patients has also been suggested.[46] Interestingly, size of the primary BCC at presentation is not always predictive of fatal outcomes but can cause significant morbidity.[39,47] 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.[48,49]

The incidence of mBCC is estimated at 0.0028%–0.5% and is quite rare.[50–54] 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.[49,52] 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.[55,56] 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.[49,52,57] 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.[58] 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.[59]

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.[3,60] 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.[4] Radiation also can play a role in primary treatment in the adjuvant setting when positive margins persist despite maximal surgical excision.[61] 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.[4,47] 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.[58] 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.[62] Further data included two CRs to single-agent cisplatin in another report, including response upon retreatment.[63] 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.[64–69] 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-fluorouracil, etoposide, methotrexate, cyclophosphamide, bleomycin, and Vinca alkaloids).[70,71] 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.[32] 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.[72,73] 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 pyelonephritis. 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.[74] 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.[75] 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.[77] All patients received vismodegib at 150 mg daily. Responses in mBCC were assessed by RECIST 1.0 criteria.[74] 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).[77] For the mBCC cohort, the median DOR was 14.8 months with a median OSof 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.[78] Additional safety and efficacy data for vismodegib has come from the

Table 1 Summary of clinical trials with hedgehog pathway inhibitors in basal cell carcinoma

Trial phase	Drug	Drug dose	Primary endpoint/ clinical intent	n	BCC status/ stage	BCC tumor shrinkage/ response	Median duration of response	Median PFS/ Median OS	Discontinued for AEs
I[72,73]	Vismodegib (GDC-0449)	Dose escalation/ expansion: 150–540 mg/D	Safety and PK-PD/ palliation	68 BCC cohort: 33	Unresectable laBCC (n=15), mBCC (n=18)	Total BCC RR: 58% (19/33) SD: 33% –laBCC RR: 60% (2 CRs) SD: 27% –mBCC RR: 50% SD: 39%	12.8 mo and ongoing	Not reported	1 withdrawal
II-ERIVANCE[76]	Vismodegib (GDC-0449)	150 mg/D	Independently assessed RR (IARR)/ palliation	104 (96 eligible for analysis)	Unresectable laBCC (n=63), mBCC (n=33)	IARR: –laBCC RR: 43% (13 CRs) SD: 38% –mBCC RR: 30% SD: 64% INV RR: –laBCC RR: 60% (13 CRs) SD: 24% –mBCC RR: 45% SD: 45%	Independent assess: laBCC: 7.6 mo mBCC: 7.6 mo INV assess: laBCC: 7.6 mo mBCC: 12.9 mo	laBCC: 9.5 mo/NM mBCC: 9.5 mo/NM	13 (12%)
Final update at 30 mo[77]						INV RR: –laBCC RR: 60.3% –mBCC 48.5%	INV assess: laBCC: 26.2 mo mBCC: 14.8 mo	laBCC: 12.9 mo/NR mBCC: 9.3 mo/ 33.4 mo	23 (22.1%)
EAP[79]	Vismodegib (GDC-0449)	150 mg/D	Efficacy, safety, and access/ palliation	120	Unresectable laBCC (n=62), mBCC (n=58)	laBCC RR: 46.4% (6 CRs) SD: 48.2% mBCC RR: 30.8% (2 CRs) SD: 51.3%	Not reported	Not reported	7
Global safety study-STEVIE[80]	Vismodegib (GDC-0449)	150 mg/D	Safety/ palliation	300	Unresectable laBCC (n=278), mBCC (n=22)	Third interim analysis (ongoing)-RR: 57.3% (44 CRs) SD: 39%	Not reported	Not reported	35 (11.7%)
I[87]	Sonedegib (LDE225)	Dose escalation/ expansion: 100–3,000 mg/D and 250–750 mg bid	Safety and PK-PD/ palliation	103 BCC cohort: 16	Unresectable laBCC, mBCC	BCC RR 37.5% (with 1 CR)	Not reported	Not reported	20 (19%)
Randomized phase II BOLT[88]	Sonedegib (LDE225)	200 mg daily vs 800 mg daily	RR per central review/ palliation	230	Unresectable laBCC (n=194), mBCC (n=36)	200 mg cohort: laBCC RR: 47% (2 CRs) SD: 44% mBCC RR: 15% SD: 77% 800 mg cohort: laBCC RR: 35% SD: 43% mBCC RR: 17% SD: 66%	200 mg cohort: laBCC: NE mBCC: NE 800 mg cohort: laBCC: NE mBCC: 8.3 mo	200 mg cohort: laBCC: NE mBCC: 13.1 mo 800 mg cohort: laBCC: NE mBCC: 7.6 mo mOS not reported	200 mg cohort: 20% 800 mg cohort: 32%

(*Continued*)

Table 1 (*Continued*)

Trial phase	Drug	Drug dose	Primary endpoint/ clinical intent	n	BCC status/ stage	BCC tumor shrinkage/ response	Median duration of response	Median PFS/ Median OS	Discontinued for AEs
I[89]	Saridegib (IPI-926)	Dose escalation/ expansion: 20–210 mg/D	Safety and PK-PD/ palliation	94 BCC cohort: 39	BCC stage: II: 26% III: 26% IV: 48%	28 evaluable and vismodegib-naïve –RR: 29% (all laBCC) (2 CRs) –SD: 68% (19/28)	9 remained on drug, including 2 >700 days	Not reported	6 (6%)
IIT[94]	Vismodegib (GDC-0449)	150 mg/D	Change in target tumor surgical defect area/ neoadjuvant	15	At least one operable primary BCC ≥5 mm	Eleven pts completed tx-27% reduction in surgical defect area from baseline	n/a	Not reported	4/14 unable to complete >3 mo of tx
Randomized II[95]	Vismodegib vs placebo (2:1)	150 mg/D	Reduction in incidence of new BCC eligible for surgery/ neoadjuvant	41	NBCCS pts with multiple primary BCCs	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 (–65% vs –11%)	n/a	Not reported	54% (14/26) on vismodegib
Exploratory II[110]	Itraconazole	200 mg vs 100 mg bid and control	Change in Ki67 and GLI1 mRNA/ neoadjuvant	29 enrolled, 19 treated	≥1 operable BCC >4 mm	45% reduction in Ki67 and 65% reduction in HH activity; 24% reduction in size of tumor	n/a	Not reported	11% (2/19)

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.

expanded access program that was launched prior to FDA approval.[79] This enrolled 120 patients (mBCC, n=58; laBCC, n=62) treated with 150 mg daily. Ninety-five patients were eligible for response evaluation, as measured by RECIST 1.0 per the treating investigator, and 119 patients were included in the safety evaluation. The median duration of vismodegib therapy was 5.5 months, but coincided with FDA approval of vismodegib. The side effects seen in the Phase II study were also seen in the expanded access program at similar rates with the majority being grade 1–2, only seven patients stopped treatment due to AEs. Serious AEs occurred in 18 patients, and included three deaths. None of the deaths were reported as related. The expanded access program confirmed the clinical benefit of vismodegib seen in prior studies: in the laBCC cohort, the RR was 46.4% (95% CI:33.0–60.3), including six CRs. Two CRs were seen in the mBCC cohort, with an objective RR of 30.8% (95% CI:17.0–47.6). Only three mBCC patients had progressive disease and none of the patients in the laBCC cohort showed progressive disease. The only factor significantly associated with RR was prior systemic therapy in the laBCC cohort, where patients who had received prior therapy had a maximal response of SD. Prior therapy included vismodegib in four patients and other SMO inhibitors in two patients.

STEVIE (NCT01367665) is a global, single-arm open-label safety study for unresectable laBCC or mBCC still accruing patients in eleven countries with safety as the primary objective.[80] The third interim analysis presented data on 300 patients, 278 with laBCC and 22 with mBCC. Similar AEs were reported: muscle spasm (59.3%), alopecia (49.3%), and dysgeusia (41%) with 17.7% treatment emergent serious adverse events. Thirty-five patients stopped treatment due to AEs, and there were 13 deaths with none clearly attributed to the study drug. The RRs were reported for all enrolled patients and included a CR rate of 17.5%, a PR rate of 39.8%, and SD in 39% echoing the low rate of progressive disease seen in other studies, confirming that almost all patients had some benefit from vismodegib.

Of note, there are now several reports of SCCs presenting in patients on vismodegib therapy.[81–85] A variety of circumstances have been described including de novo keratoacanthomas, invasive SCCs arising from pre-existing actinic keratosis, possible collision lesions with regression of the BCC and growth of the remaining SCC component, or possible evolution of BCC into SCC. At this time, there is no conclusive evidence of SMO inhibitors inducing new cancers. One postulate is that decreased HH signaling may drive SCC carcinogenesis.[86]

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 for 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.[95] 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.[96] 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.[97] 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.[95,98] 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.[99] He had a baseline W844C mutation in *PTCH1*. 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.[100] Tumor resistance to vismodegib subsequently was described in six laBCC patients but no analyses were done.[101] 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.[102] 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.[103] 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.[104] 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 immunohistochemcial.[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.

Disclosure

LAF has received research funding from Merck, Sanofi-Aventis, and Genentech-Roche and served as a consultant for Genentech-Roche and Bristol-Myer Squibb. WHS has served as a consultant to Merck, Genentech, and Castle Biosciences and has received funding for research from Bristol-Myers Squibb. The authors report no other conflicts of interest in this work.

References

1. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol*. 2010;146(3):283–287.
2. Lomas A. A systematic review of worldwide incidence of NMSC. *Br J Dermatol*. 2012;166:1069–1080.
3. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005;353(21):2262–2269.
4. Veness MJ. The important role of radiotherapy in patients with nonmelanoma skin cancer and other cutaneous entities. *J Med Imaging Radiat Oncol*. 2008;52(3):278–286.
5. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol*. 1995;131:157–163.
6. Kricker A, Armstrong BK, English DR, Heenan PJ. A dose–response curve for sun exposure and basal cell carcinoma. *Int J Cancer*. 1995; 60(4):482–488.

7. Silverman MK, Kopf AW, Grin CM, et al. Recurrence rates of treated basal cell carcinomas. Part 1: Overview. *J Dermatol Surg Oncol*. 1991; 17(9):713–718.
8. Dreier J, Cheng PF, Bogdan Alleman I, et al. Basal cell carcinomas in a tertiary referral centre-a systematic analysis. *Br J Dermatol*. 2014; 171(5):1066–1072. Epub June 28, 2014.
9. Zhang M, Qureshi AA, Geller AC, et al. Use of tanning beds and incidence of skin cancer. *J Clin Oncol*. 2012;30(14):1588–1593.
10. Wehner MR, Shive ML, Chren MM, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. *BMJ*. 2012;345:e5909.
11. Karagas MR, McDonald JA, Greenberg ER, et al. For the Skin Cancer Prevention Study Group. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. *J Natl Cancer Inst*. 1996;88(24): 1848–1853.
12. Mizuno, Tokuoka S, Kishikawa M, Nakashima E, Mabuchi K, Iwamoto KS. Molecular basis of basal cell carcinogenesis in the atomic-bomb survivor population: p53 and PTCH gene alterations. *Carcinogenesis*. 2006;27(11):2286–2294.
13. Lear JT, Tan BB, Smith AG, et al. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. *J R Soc Med*. 1997;90(7): 371–374.
14. Wilkins K, Turner R, Dolev JC, et al. Cutaneous malignancy and human immunodeficiency virus disease. *J Am Acad Dermatol*. 2006;54: 189–206.
15. Silverberg MJ, Leyden W, Warton EM, et al. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. *J Natl Cancer Inst*. 2013;105:350–360.
16. Tessari G, Girolomoni G. Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors and management. *Derm Surg*. 2012;38(10):1622–1630.
17. Castori M, Morrone A, Kanitakis J, et al. Genetic skin diseases predisposing to basal cell carcinoma. *Eur J Dermatol*. 2012;22(3): 299–309.
18. Gorlin RJ. Nevoid basal-cell carcinoma syndrome. *Medicine*. 1987;66: 98–113.
19. Gorlin, RJ. Nevoid basal cell carcinoma syndrome. *Dermatol. Clin*. 1995;13:113–125.
20. Hahn H, Wicking C, Zaphiropoulous PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell*. 1996;85:841–851.
21. Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science*. 1996;272: 1668–1671.
22. Lin TL, Matsui W. Hedgehog pathway as a drug target: smoothened inhibitors in development. *OncoTargets and Therapy*. 2012;5: 47–58.
23. Brechbiel J, Miller-Moslin K, Adjei A. Crosstalk between hedgehog and other signaling pathways as a basis for combination therapies in cancer. *Cancer Treat Rev*. 2014;40(6):750–759.
24. Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. *J Invest Dermatol*. 1998;110:885–888.
25. Wolter M, Reifenberger J, Sommer C, et al. Mutations in the human homologue of the Drosophila segment polarity gene patched (PTCH) in sporadic basal cell carcinomas of the skin and primitive neuroectodermal tumors of the central nervous system. *Cancer Res*. 1997;57(13):2581–2585.
26. Xie J, Murone M, Luoh SM, et al. Activating smoothened mutations in sporadic basal-cell carcinoma. *Nature*. 1998;391(6662):90–92.
27. Ling G, Ahmadian A, Persson A, et al. PATCHED and p53 gene alterations in sporadic and hereditary basal cell cancer. *Oncogene*. 2001;20:7770–7778.
28. Reifenberger J, Wolter M, Knobbe CB, et al. Somatic mutations in the PTCH, SMOH, SUFUH and TP53 genes in sporadic basal cell carcinomas. *Br J Dermatol*. 2005;152(1):43–51.
29. Daya-Grosjean L, Sarasin A. UV-specific mutations of the human patched gene in basal cell carcinomas from normal individuals and xeroderma pigmentosum patients. *Mutation Research*. 2000;450:193–199.
30. Keeler RF. Cyclopamine and related steroidal alkaloid teratogens: their occurrence, structural relationship, and biologic effects. *Lipids*. 1978;13(10):708–715.
31. Chen JK, Taipale J, Cooper MK, et al. Inhibition of Hedgehog signaling by direct binding of cyclopamine to Smoothened. *Genes Dev*. 2002;16:2743–2748.
32. Robarge KD, Brunton SA, Castanedo GM, et al. GDC-0449-a potent inhibitor of the hedgehog pathway. *Bioorg Med Chem Lett*. 2009;19: 5576–5581.
33. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55(3):490–500.
34. Cakir BO, Adamson P, Cingi C. Epidemiology and economic burden of nonmelanoma skin cancer. *Facial Plast Surg Clin North Am*. 2012;20(4):419–422.
35. Gordon LG, Scuffham PA, van der Pols JC, McBride P, Williams GM, Green AC. Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. *J Invest Dermatol*. 2009;129: 2766–2771.
36. Mudigonda T, Levender MM, O'Neill JL, West CE, Pearce DJ, Feldman SR. Incidence, risk factors, and preventative management of skin cancers in organ transplant recipients: a review of single- and multicenter retrospective studies from 2006 to 2010. *Dermatol Surg*. 2013;39(3 Pt 1): 345–364. Epub November 27, 2012.
37. US Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent Skin Cancer*. Washington, DC: US Dept of Health and Human Services, Office of the Surgeon General; 2014. Available from: http://www.surgeongeneral.gov/library/calls/prevent-skin-cancer/call-to-action-prevent-skin-cancer.pdf. Accessed October 11, 2014.
38. International Agency for Research on Cancer and the World Health Organization. *European Code Against Cancer*. Lyon, France. Available from: http://www.europeancancerleagues.org/images/European_Code_Against_Cancer/sans_WM_01a_Level1NEW_logo_EN.pdf. Accessed October 11, 2014.
39. Ionescu DN, Arida M, Jukic D. Metastatic Basal Cell Carcinoma: four case reports, review of literature, and immunohistochemical evaluation. *Arch Pathol Lab Med*. 2006;130:45–51.
40. Menz J, Sterrett G, Wall L. Metastatic basal cell carcinoma associated with a small primary tumour. *Australas J Dermatol*. 1985;26:121–124.
41. Walling HW, Fosko SW, Geraminejad PA, et al. Aggressive basal cell carcinoma: presentation, pathogenesis, and management. *Cancer Metastasis Rev*. 2004;23(3–4):389–402.
42. Dixon AY, Lee SH, McGregor DH. Histologic features predictive of basal cell carcinoma recurrence: results of a multivariate analysis. *J Cutan Pathol*. 1993;20(2):137–142.
43. Farmer ER, Helwig EB. Metastatic basal cell carcinoma: a clinicopathologic study of seventeen cases. *Cancer*. 1980;46:748–757.
44. Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. *J Dermatol Surg Oncol*. 1992;18(6):471–476.
45. Kinoshita R, Yamamoto O, Yasuda H, et al. Basal cell carcinoma of the scrotum with lymph node metastasis: report of a case and review of the literature. *Int J Dermatol*. 2005;44(1):54–56.
46. Hausauer AK, Maurer T, Leslie KS, et al. Recurrence after treatment of cutaneous basal cell and squamous cell carcinomas in patients infected with human immunodeficiency virus. *JAMA Dermatol*. 2013; 149(2):239–241.
47. Zoccali G, Pajand R, Papa P, et al. Giant basal cell carcinoma of the skin: literature review and personal experience. *J Eur Acad Dermatol Venereol*. 2012;26(8):942–952.
48. Weinstock MA, Bogaars HA, Ashley M, et al. Nonmelanoma skin cancer mortality: a population-based study. *Arch Dermatol*. 1991;127: 1194–1197.

49. Wysong A, Aasi SZ, Tang JY. Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. *JAMA Dermatol*. 2013 149(5):615–616.
50. Paver K, Poyzer K, Burry N, et al. Letter: the incidence of basal cell carcinoma and their metastases in Australia and New Zealand. *Australas J Dermatol*. 1973;14:53.
51. Mikhail GR, Nims LP, Kelly AP Jr, et al. Metastatic basal cell carcinoma: review, pathogenesis, and report of two cases. *Arch Dermatol*. 1977;113:1261–1269.
52. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma: report of five cases and review of 170 cases in the literature. *J Am Acad Dermatol*. 1984;10:1043–1060.
53. Lo JS, Snow SN, Reizner GT, et al. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol*. 1991;24:715–719.
54. Snow SN, Sahl W, Lo JS, et al. Metastatic basal cell carcinoma: report of five cases. *Cancer*. 1994;73:328–335.
55. Farasat S, Yu SS, Neel VA, et al. A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: creation and rationale for inclusion of tumor (T) characteristics. *J Am Acad Dermatol*. 2011;64(6):1051–1059.
56. Thacker CA, Weiss GJ, Tibes R, et al. 18-FDG PET/CT assessment of basal cell carcinoma with vismodegib. *Cancer Med*. 2012;1(2): 230–236.
57. Raszewski RL, Guyuron B. Long-term survival following nodal metastases from basal cell carcinoma. *Ann Plast Surg*. 1990;24:170–175.
58. Danial C, Lingala B, Balise R, et al. Markedly improved overall survival in 10 consecutive patients with metastatic basal cell carcinoma. *Br J Dermatol*. 2013;169:673–676.
59. Lewis KD, Sekulic A, Hauschild A, et al. Vismodegib in the treatment of patients with metastatic basal cell carcinoma (mBCC) and distant metastases: survival in the pivotal phase II and phase I studies [abstract]. *J Clin Oncol*. 2014;32:5s(Suppl; abstr 9012).
60. Bath-Hextall FJ, Perkins W, Bong J, et al. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev*. 2007; 24:(1):CD003412.
61. National Comprehensive Cancer Network. *Basal Cell Skin Cancer*. (Version 1.2015). Available from: http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf. Accessed April 3, 2015.
62. Salem P, Hall SW, Benjamin RS, et al. Clinical phase I–II study of cis-dichloro-diammineplatinum(II) given by continuous lv infusion. *Cancer Treat Rep*. 1978;62:1553–1555.
63. Khandekar JD. Complete response of metastatic basal cell carcinoma to cisplatin chemotherapy: a report on two patients. *Arch Dermatol*. 1990;126(12):1660.
64. Woods RL, Stewart JF. Metastatic basal cell carcinoma: report of a case responding to chemotherapy. *Postgrad Med J*. 1980;56:272–273.
65. Wieman TJ, Shively EH, Woodcock TM. Responsiveness of metastatic basal-cell carcinoma to chemotherapy: a case report. *Cancer*. 1983;52:1583–1585.
66. Guthrie TH Jr, McElveen LJ, Porubsky ES, et al. Cisplatin and doxorubicin. An effective chemotherapy combination in the treatment of advanced basal cell and squamous carcinoma of the skin. *Cancer*. 1985;55(8):1629–1632.
67. Guthrie TH Jr, Porubsky ES, Luxenberg MN, et al. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. *J Clin Oncol*. 1990;8(2):342–346.
68. Jefford M, Kiffer JD, Somers G, et al. Metastatic basal cell carcinoma: rapid symptomatic response to cisplatin and paclitaxel. *ANZ J Surg*. 2004;74:704–705.
69. Carneiro BA, Watkin WG, Mehta UK, et al. Metastatic basal cell carcinoma: complete response to chemotherapy and associated pure red cell aplasia. *Cancer Invest*. 2006;24(4):396–400.
70. Pfeiffer P, Hansen O, Rose C. Systemic cytotoxic therapy of basal cell carcinoma. A review of the literature. *Eur J Cancer*. 1990;26: 73–77.
71. Moeholt K, Aagaard H, Pfeiffer P, et al. Platinum-based cytotoxic therapy in basal cell carcinoma – a review of the literature. *Acta Oncol*. 1996;35:677–682.
72. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med*. 2009;361:1164–1172.
73. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. *Clin Cancer Res*. 2011;17:2502–2511.
74. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205–216.
75. LoRussoPM, Jimeno A, Dy G, et al. Pharmakokinetic dose-scheduling study of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors. *Clin Cancer Res*. 2011;17:5774–5782.
76. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366: 2171–2179.
77. Sekulic A, Migden MR, Basset-Seguin N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update (30-month) of the pivotal ERIVANCE BCC study [abstract]. *J Clin Oncol*. 2014;32:5s(Suppl; abstr 9013).
78. Sekulic A, Hainsworth JD, Lewis KD, et al. Vismodegib for advanced basal cell carcinoma: Duration of response after vismodegib discontinuation and response to vismodegib retreatment upon disease progression [abstract]. *J Clin Oncol*. 2014;32:5s(Suppl; abstr 9081).
79. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the hedgehog pathway inhibitor, vismodegib. *J Am Acad Dermatol*. 2014;70:60–69.
80. Grob JJ, Kunstfeld R, Dreno B, et al. Vismodegib, a Hedgehod pathway inhibitor (HPI), in advanced basal cell carcinoma (aBCC): STEVIE study interim analysis in 300 patients [abstract]. *J Clin Oncol*. 2013; 31(Suppl; abstr 9036).
81. Larrobino A, Messina JL, Kudchadkar R, Sondak VK. Emergence of a squamous cell carcinoma phenotype following treatment of metastatic basal cell carcinoma with vismodegib. *J Am Acad Dermatol*. 2013;69(1):e33–e34.
82. Aasi S, Silkiss R, Tang JY, et al. New onset of keratoacanthomas after vismodegib treatment for locally advanced basal cell carcinomas: a report of 2 cases. *JAMA Dermatol*. 2013;149(2):242–243.
83. Zhu GA, Sundrum U, Chang AL. Two different scenarios of squamous cell carcinoma within advanced basal cell carcinomas. *JAMA Dermatol*. 2014;150(9):970–973.
84. Orouji A, Goerdt S, Utikal J, Leverkus M. Multiple highly and moderately differentiated squamous cell carcinomas of the skin during vismodegib treatment of inoperable basal cell carcinoma. *Br J Dermatol*. 2014;171(2):431–433. Epub August 2, 2014.
85. Saintes C, Saint-Jean M, Brocard A, et al. Development of squamous cell carcinoma into basal cell carcinoma under treatment with vismodegib. *JEADV*. Epub July 1, 2014. 2015 May;29(5):1006–1009. doi: 10.1111/jdv.12526.
86. Wakabayashi Y, Mao JH, Brown K, Girardi M, Balmain A. Promotion of Hras-induced squamous carcinomas by a polymorphic variant of the patched gene in FVB mice. *Nature*. 2007;445(7129):761–765. Epub January 17, 2007.
87. Rodon J, Tawbi HA, Thomas AL, et al. A phase I, multicenter, open-label, first-in-human, dose escalation study of the oral smoothened inhibitor sonidegib (LDE225) in patients with advanced solid tumors. *Clin Ca Res*. 2014;20(7);1900–1909.
88. Migden MR, Guminski AD, Gutzmer, et al. Randomized, double-blind study of sonidegib (LDE225) in patients with locally advanced or metastatic basal-cell carcinoma [abstract]. *J Clin Oncol*. 2014;32: 5s(Suppl; abstr 9009a).

89. Jimeno A, Weiss GJ, Miller WH, et al. Phase I study of the hedgehog pathway inhibitor IPI-926 in adult patients with solid tumors. *Clin Cancer Res*. 2013;19(10):2766–2774.
90. Infinity Pharmaceuticals. Annual Report 2012. Cambridge, MA. Available from: http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NTAzMDc5fENoaWxkSUQ9NTQzODAxfFR5cGU9MQ==&t=1. Accessed September 9, 2013.
91. Siu LL, Papadopoulos N, Alberts SR, et al. A first-in-human, phase I study of an oral hedgehog (HH) pathway antagonist, BMS-833923 (XL139), in subjects with advanced or metastatic solid tumors [abstract]. *J Clin Oncol*. 2010;28:15s(Suppl; abstr 2501).
92. Peukert S, He F, Dai M, et al. Discovery of NVP-LEQ506, a second-generation inhibitor of smoothened. *Chem Med Chem*. 2013;8:1261–1265.
93. Ishii T, Shimizu Y, Nakashima K, et al. Inhibition mechanism exploration of investigational drug TAK-441 as inhibitor against vismodegib-resistant smoothened mutant. *Eur J Pharmacol*. 2014;15;723:305–313.
94. Ally MS, Aasi S, Wysong A, et al. An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. *J Am Acad Dermatol*. 2014;71(5):904–911. e1. Epub June 11, 2014.
95. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med*. 2012;366:2180–2188.
96. Skvara H, Kalthoff F, Meingassner JG, et al. Topical treatment of basal cell carcinomas in nevoid basal cell carcinoma syndrome with a smoothened inhibitor. *J Invest Dermatol*. 2011;131(8):1735–1744.
97. Novartis Pharmaceuticals. Key developments in the fourth quarter of 2011; 2011. Basel, Switzerland. Available from: http://www.novartis.com/downloads/investors/financial-results/q4-2011-innovation-tables.pdf. Accessed September 9, 2013.
98. Wolfe CM, Green WH, Cognetta AB Jr, et al. Basal cell carcinoma rebound after cessation of vismodegib in a nevoid basal cell carcinoma syndrome patient. *Dermatol Surg*. 2012;38(11):1863–1866.
99. Rudin CM, Hann CL, Laterra J, et al. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. *N Engl J Med*. 2009;361:1173–1178.
100. Yauch RL, Dijkgraaf GJ, Alicke B, et al. Smoothened mutation confers resistance to a hedgehog pathway inhibitor in medulloblastoma. *Science*. 2009;326:572–574.
101. Chang AL, Oro AE. Initial assessment of tumor regrowth after vismodegib in advanced basal cell carcinoma. *Arch Dermatol*. 2012;148(11):1324–1325.
102. Brinkhuizen T, Reinders MG, van Geel M, et al. Acquired resistance to the hedgehog pathway inhibitor vismodegib due to smoothened mutations in treatment of locally advanced basal cell carcinoma. *J Am Acad Dermatol*. 2014;71(5):1005–1008.
103. Meani RE, Lim, Chang AL, et al. Emergence of chemoresistance in a metastatic basal cell carcinoma patient after complete response to hedgehog pathway inhibitor vismodegib (GDC-0449). *Australian J Dermatol*. 2014;55:218–221.
104. Sharpe HJ, Pau G, Dijkgraaf, et al. Genomic analysis of smoothened inhibitor resistance in basal cell carcinoma. *Cancer Cell*. 2015;27:327–341.
105. Rudin CM. Vismodegib. *Clin Ca Res*. 2012;18(12):3218–3222.
106. Dijkgraaf GJ, Alicke B, Weinmann L, et al. Small molecule inhibition of GDC-0449 refractory smoothened mutants and downstream mechanisms of drug resistance. *Cancer Res*. 2011; 71:435–444.
107. Buonamici S, Williams J, Morrissey M, et al. Interfering with resistance to smoothened antagonists by inhibition of the PI3K pathway in medulloblastoma. *Sci Transl Med*. 2010;2:51–70.
108. Kim J, Tang JY, Gong R, et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell*. 2010;17(4):388–399.
109. Kim D, Kim J, Aftab BT, Tang JY, et al. Itraconazole and arsenic trioxide inhibit hedgehog pathway activation and tumor growth associated with acquired resistance to smoothened inhibitors. *Cancer Cell*. 2013;23(1):23–34.
110. Kim DJ, Kim J, Spaunhurst K, et al. Open–label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. *J Clin Oncol*. 201410;32(8):745–751. Epub February 3, 2014.
111. Bijlsma MF, Spek CA, Zivkovic D, van de Water S, Rezaee F, Peppelenbosch MP. Repression of smoothened by patched-dependent (pro-)vitamin D3 secretion. *PLoS Biol*. 2006;4(8):e232.
112. Uhmann A, Niemann H, Lammering B, et al. Antitumoral effects of calcitriol in basal cell carcinomas involve inhibition of Hedgehog signaling and induction of vitamin D receptor signaling and differentiation. *Mol Cancer Ther*. 2011;10(11):2179–2188.
113. Ning H, Mitsui H, Wang CQF, et al. Identification of anaplastic lymphoma kinase as a potential therapeutic target in basal cell carcinoma. *Oncotarget*. 2013;4(12):2237–2248.
114. Morinello E, Pignatello M, Villabruna L, Goelzer P, Bürgin H. Embryofetal development study of vismodegib, a hedgehog pathway inhibitor, in rats. *Birth Defects Res B Dev Reprod Toxicol*. 2014;101(2):135–143. Epub April 1, 2014.
115. Mohan SV, Chang AL. Management of cutaneous and extracutaneous side effects of smoothened inhibitor therapy for advanced basal cell carcinoma. *Clin Cancer Res*. June 15, 2015;21(12):2677–2683. Epub 2015 Mar 19.

Biologics: Targets & Therapy

Dovepress

Publish your work in this journal

Biologics: Targets & Therapy is an international, peer-reviewed journal focusing on the patho-physiological rationale for and clinical application of Biologic agents in the management of autoimmune diseases, cancers or other pathologies where a molecular target can be identified. This journal is indexed on PubMed Central, CAS, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/biologics-targets--therapy-journal