Management of Cutaneous and Extracutaneous Side Effects of Smoothened Inhibitor Therapy for Advanced Basal Cell Carcinoma

Shalini V. Mohan and Anne Lynn S. Chang

Stanford University School of Medicine, Department of Dermatology, Redwood City, California.

Corresponding Author: Anne Lynn S. Chang, Stanford University School of Medicine, Department of Dermatology, 450 Broadway Street, MC 5334, Pavilion C, 2nd Floor, Redwood City, CA 94063. Phone: 650-721-7151; Fax 650-721-3464; E-mail: alschang@stanford.edu

Running Title: Management of Side Effects of SMO inhibitor Therapy for aBCC

Disclosure of Potential Conflicts of Interest

A.L.S. Chang reports receiving commercial research grants from Eli Lilly, Genentech/Roche, and Novartis Pharmaceuticals Corporation, and is a consultant/advisory board member for Genentech/Roche and Novartis Pharmaceuticals Corporation. No potential conflicts of interest were disclosed by the other author.
Abstract

Smoothened inhibitors represent the first class of targeted drugs approved for use in advanced and metastatic basal cell carcinoma. For many patients with limited treatment options, this drug class has led to significant clinical improvements, but is not without side effects. In this review, we outline the basic mechanism of smoothened inhibitors and the most commonly observed cutaneous and extracutaneous side effects. We also highlight possible mechanisms for these adverse events and current management strategies.
Introduction

Smoothened inhibitors (SIs) are a class of drugs newly approved by the FDA for use in advanced basal cell carcinomas (BCCs). Because BCCs are the most common human malignancy worldwide, with an age-adjusted incidence of 1000 to 1500 per 100,000 adults in the United States (1), the ability to suppress their growth in a targeted fashion is a highly significant step forward in cutaneous oncology.

Smoothened (SMO) is a 7-transmembrane protein in the hedgehog (Hh) signaling pathway that when aberrantly activated can function as an oncogene by promoting unregulated activation of the Hh pathway (2-4). The Hh signaling pathway is responsible for midline embryonic development and is generally silenced in adults except for activity in hair follicles and taste buds (5-11). Aberrant activation of this pathway results in tumorigenesis and is associated with BCCs and medulloblastoma (2-4, 6, 7). SIs block Hh signaling, leading to suppression of tumor growth and tumor regression (12-17). Although there are many potential targets within this pathway, most compounds in clinical development that block Hh signaling target SMO, including vismodegib (GDC-0449), which is already commercially available (18). Other SIs currently being studied in clinical trials include sonidegib (LDE225), saridegib (IPI-926), and BMS-833923 (XL139) (12-15, 17).

A number of cutaneous and extracutaneous side effects of SIs have been reported (12, 14-17, 19), although few studies have been conducted on the mechanisms of the clinical side effects in humans. Nevertheless, data on the function of the Hh pathway from preclinical animal models and the limited clinical trials in humans lend insight into how SIs may exert their toxicities (8, 20-31). While data are still being collected on side effects specific to individual SIs, several side effects, such as hair loss, muscle spasms, and gastrointestinal (GI) and taste disturbances, are...
common to several SIs and are likely class effects. Adverse effects (AEs) may be significant enough to lead to drug discontinuation (15, 16, 32), and therefore the ability to adequately manage these AEs is crucial to treatment adherence and patient quality of life. The significance of these side effects and lack of effective treatment options for these drug toxicities are illustrated in the pivotal phase 2 study of vismodegib, in which 12% of advanced BCC patients discontinued treatment due to an AE (16), and more recently in an international study with a 30-month follow-up in which 22.1% of advanced BCC patients discontinued treatment due to an AE (32). To date, there is no evidence that SI-induced cutaneous or extracutaneous side effects correlate with drug response, unlike other targeted therapies such as epidermal growth factor receptor inhibitors, for which an acne-like rash is associated with tumor response (33).

Although not discussed in this review, SIs are potent teratogens that lead to severe midline defects in the developing fetus and are not to be used in females of childbearing potential or male partners of females of childbearing potential who do not agree to use two forms of reliable contraception (34).

Because of dose effects of drug toxicities, this review considers the rates of side effects based on phase 2 and/or FDA-approved dose whenever possible. Long-term data on AEs are still being collected as more patients are exposed to SIs, but high quality data are available for some of these drugs through phase 1 and 2 clinical trials (12-17, 19, 35). The side effects discussed here were selected based on literature reports and incidence and are not meant to be comprehensive.

**Cutaneous Adverse Effects of Smoothened Inhibitors**

**Hair loss**
Approximately 15% to 60% of patients treated with SIs experienced alopecia within 2 to 4 months of initiating SI therapy; exact rates depend on the specific SI (Table 1) (12-17, 21, 30, 35-43). Alopecia is reported more frequently with vismodegib than other SIs, with up to 58% and 63% of patients affected in phase 1 and 2 trials, respectively (16, 19, 35, 43). A phase 2 study of sonidegib revealed an alopecia incidence rate of 43% at the 200-mg daily dosage (12, 13). SI-related alopecia is reported to affect eyebrows, eyelashes, and body hair, although our clinical observations have shown that some patients with hair loss in one anatomic location may be spared hair loss in other locations. In humans, the Hh pathway is reported to maintain bulge cell phenotype and is likely needed for normal hair follicle regeneration (30). SI-related alopecia is reversible following discontinuation of the drug, with patients seeing evidence of regrowth after 4 to 6 weeks (42).

**Hypersensitivity reaction**

Two cases of patients experiencing drug hypersensitivity reactions following treatment with vismodegib were recently reported (Table 1) (41, 42). One report describes a 77-year-old woman being treated with vismodegib for numerous and recurrent BCCs who developed on-target side effects in addition to sudden onset of fevers, chills, myalgia, and fatigue 3 weeks after drug initiation (41). Treatment was discontinued, and laboratory testing revealed elevated liver function and hypereosinophilia. These laboratory values normalized 10 days after discontinuation of vismodegib. Kwong et al. reported a case of a man in his 50s who developed erythematous dermal plaques on his arms and chest after 8 months of treatment with vismodegib (42). The patient was not exposed to any other medications or drugs during treatment with vismodegib. A skin biopsy confirmed superficial and deep perivascular dermatitis with eosinophils, consistent with a cutaneous drug eruption. The patient was treated with topical...
steroids and did not need to discontinue vismodegib. The exact incidence of dermal hypersensitivity reaction in patients being treated with vismodegib is unclear and likely to be < 20% as rash was not one of the common side effects in the phase 2 study that led to FDA approval (16).

**Squamous cell carcinoma and keratoacanthoma**

One potential concern with the use of targeted therapies is the possibility that abrogation of one pathway may lead to activation of another. Recently, a case report has been published that describes patients without a history of squamous cell carcinoma (SCC) who developed keratoacanthoma (a low-grade variant of SCC originating from hair follicles) immediately after initiation of vismodegib for locally advanced BCC (laBCC; Table 1) (36). Other reports have described patients who developed cutaneous SCC following vismodegib treatment, both as new tumors and as lesions within the existing laBCC tumor bed (37-40). In a recent international study of 104 patients receiving vismodegib for advanced BCC, 11% developed SCC (32).

The etiology of this connection may be multifactorial and can be thought of on both a cellular and clinical level. On a cellular level, SMO inhibition may select for tumor cells that are not driven by the Hh pathway, including SCCs (18, 40). On a clinical level, ultraviolet light (UV) exposure is a common risk factor for both BCC and SCC (44); therefore, individuals exposed to high levels of UV may develop both types of skin cancer. In addition, patients receiving SIs may have more frequent or more complete skin examinations, which may lead to a detection bias. Although no data from randomized trials currently exist to support this hypothesis, long-term outcomes studies are underway that may help to answer this question. Because of the possibility of new-onset SCCs after initiation of SIs, total body skin examinations with a low threshold to biopsy new suspicious lesions appears prudent.
Extracutaneous Adverse Effects of Smoothened Inhibitors

Gastrointestinal toxicity (nausea, vomiting, diarrhea, and constipation)

Nausea and vomiting were the most common GI toxicities, affecting up to one-third of patients receiving vismodegib, sonidegib, or saridegib (Table 2) (12-16, 35). Based on data from 198 patients enrolled in phase 1 and 2 trials of vismodegib, 95% of patients experienced grade 1 or 2 GI disturbances, including nausea, vomiting, diarrhea, constipation, and pain (45). Grade 3 or 4 GI irritation was reported in 10% of patients (45). In a phase 2 trial of sonidegib, 33% of patients treated with the 200-mg daily dosage experienced nausea (12, 13). Only 3 of 28 patients exposed to varying doses of BMS-833923 in a phase 1 study reported nausea (17). There are no formal studies to date examining the efficacy of currently available antiemetics for SI-induced nausea or vomiting. Anecdotally, medications such as ondansetron or metoclopramide have been used and can provide significant relief. SI-related diarrhea and constipation can be reduced or resolved with loperamide or stool softeners, respectively, although no formal studies have been conducted to identify the agents that are most effective in reducing or eliminating these side effects.

The Hh pathway is highly expressed in the GI epithelium and plays an important role in function and repair (5). In animal models, paracrine Hh signaling has been demonstrated from the stomach to the colon and has been found to be important in modulating villus core smooth muscle (23). Disruption of this pathway through SIs may explain the GI side effects of nausea, vomiting, diarrhea, and constipation (27).

Amenorrhea

Amenorrhea or menstrual irregularity has been reported in women of childbearing potential taking vismodegib (Table 2) (35, 46). For instance, in an expanded access study of vismodegib, 4 of 8 women of childbearing age experienced irregular menses or amenorrhea while on
vismodegib (35). In this small number of patients, there were no clear differences in weight loss or hormonal birth control use between those who did or did not experience menstrual irregularity. Strasswimmer and colleagues reported a case of a 34-year-old patient who developed amenorrhea one month after starting vismodegib and resumed menses 5 weeks after discontinuation (46). After hormonal evaluation, this patient’s amenorrhea was attributed to blockade of follicle-stimulating hormone-receptor–dependent signal transduction at the level of the ovaries. While the exact mechanism of amenorrhea remains to be further clarified, an alternative hypothesis might involve SI effects on the uterus—the exogenous hormone-induced menses of a patient treated in our practice with a prior bilateral oophorectomy ceased after initiation of SI therapy. To date, we are not aware of any cases where menstrual cycles did not resume after vismodegib cessation.

Dysgeusia
Taste disturbance or dysgeusia was reported within the first 1 to 2 months following SI initiation in 16.7% to 70.6% of patients, depending on the particular SI used (Table 2) (12-17, 20, 25, 29, 31, 35, 46-49). While not formally studied, dysgeusia’s contribution to lack of appetite has been suggested by clinical observation. Grade 2 dysgeusia includes altered taste with change in diet (per Common Terminology Criteria for Adverse Events version 4 (50)), potentially leading to weight loss, an adverse event also associated with SIs (12, 13, 16, 35). Sonidegib and saridegib had the lowest reported dysgeusia incidence rates with 16.7 to 38% and 27.8%, respectively (12-15). In our clinical experience and as reported in the Basal Cell Nevus Network patient support group newsletter, patients experience a metallic or bland taste associated with most food and beverages (51). Patient-reported suggestions for coping with SI-related dysgeusia include
consumption of spicy, sweet, cold, or acidic foods and use of baking soda as a mouth rinse prior to eating (51).

Data from preclinical animal models provide evidence to suggest that dysgeusia is an on-target effect of Hh pathway inhibition (20, 22, 24, 26). Sonic Hh (Shh)–responsive cells maintain the taste buds and filiform and fungiform papillae, all of which play a role in taste (20, 22, 24, 26). Inhibition of Shh signaling through SIs likely leads to disruption of these structures, thus accounting for the dysgeusia observed in patients treated with SIs.

**Myopathy (including symptoms of muscle spasms and muscle pain [myalgia])**

Myopathy is one of the most common AEs of SIs (12-14, 16, 35, 44), with up to 71% of patients treated with vismodegib, 50% of patients treated with sonidegib, 33% of patients treated with saridegib, and 44% of patients treated with BMS-833923 having reported muscle spasms (Table 2) (12-14, 16, 17, 35, 44). Clinically, myopathy is often one of the first AEs to be reported (35). Many of our patients on vismodegib indicated myopathy can significantly impact patient quality of life and may even lead patients to discontinue treatment with SIs. There is little evidence to suggest that a correlation exists between the symptoms of myopathy and elevated creatine kinase (CK) levels. Oral muscle relaxants (e.g., cyclobenzaprine) may transiently decrease the severity or number of muscle spasms; however, future studies are needed to identify the best method of treating this common side effect. Levocarnitine, an amino acid derivative that is commercially available as a supplement, is currently being tested in a randomized, double-blind, placebo-controlled trial in patients with vismodegib-associated muscle spasms (NCT01893892) based on anecdotal patient reports of decreased muscle spasm frequency and severity while taking this agent.
The mechanism of myopathy in humans taking SIs has not been established. In animal models, activation of the Shh pathway promotes regeneration of myofibers (25, 29, 31); therefore, inhibition of the pathway with SIs may impede muscle repair.

**Elevated creatine kinase**

Currently, the incidence of CK elevations appears to vary with the different SIs. Assessment of CK levels was not included in vismodegib clinical trial protocols; therefore, the incidence of elevated CK in these studies is unclear. Vismodegib does not require monitoring of CK levels based on the package insert (3); however, patients with risk factors for CK elevation may be considered for monitoring, as elevated CK has been reported with vismodegib treatment (52, 53). For instance, our clinical experience in patients taking multiple medications suggest that CK elevation may occur in rare instances and is reversible upon discontinuation of vismodegib. In contrast, studies of sonidegib included CK monitoring, which has been shown to result in grade 2 to 4 CK elevation in up to 29% of patients (Table 2), with or without clinical symptoms, in a dose-dependent fashion (12, 13). The incidence of CK elevation in patients exposed to saridegib or BMS-833923 in phase 1 studies was not reported (14). CK monitoring may be considered in individuals with risk factors for rhabdomyolysis, such as alcohol abuse, concomitant medications (including HMG-CoA reductase inhibitors, itraconazole, cyclosporine, colchicine, and erythromycin), overexertion, or muscular dystrophy (54, 55), although evidence-based guidelines currently do not exist for this practice.

Although there is no clear association between muscle spasm or myalgia symptoms and CK elevations, it could be hypothesized that CK elevation may result from impaired repair of cellular muscle damage, as discussed in the section on myopathy (29, 31).

**Hepatotoxicity**
Hepatotoxicity in the form of transaminitis or cholestasis has been reported in patients being treated with SIs (Table 2) (12-17, 20, 25, 29, 31, 35, 46-49). For vismodegib, the rate of occurrence did not exceed 30% (47, 48). Similar effects were seen with saridegib in patients with solid tumors, in whom the major dose-limiting toxicity was transient and reversible grade 3 alanine aminotransferase and/or aspartate aminotransferase elevation at the phase 2 dose of 160 mg/day (1 of 18 patients [6%]) (14). Some of the reported cases of hepatotoxicity occurring in patients being treated with SIs may be due to concomitant use of medications that may also contribute and thus enhance this side effect. For instance, elevated liver enzymes and cholestasis was reported in an individual on vismodegib therapy after starting a nonsteroidal anti-inflammatory drug for muscle spasms (48). Postmarketing data for vismodegib based on a summary from the FDA Adverse Events Reporting System spanning January 2012 to January 2013 revealed 15 cases of hepatotoxicity, including elevated liver enzymes or bilirubin, hepatitis, and hepatocellular damage (47). These cases included patients taking vismodegib with other known hepatotoxic drugs, such as erlotinib and acetaminophen (56, 57). Although additional data are needed to provide guidance on laboratory monitoring for patients on SI therapy, periodic laboratory monitoring may be considered in those taking potentially hepatotoxic medications.

The Hh pathway is important in the hepatic repair response following chronic liver injury in human liver cells (28); therefore, inhibition of Hh signaling may prevent repair of adult liver injuries. However, the specific mechanism of SI-associated hepatotoxicity has not been reported.

Weight loss

Weight loss associated with SI treatment may be multifactorial in origin, including decreased oral intake from dysgeusia, GI toxicity, and/or advanced BCC. Compared to other toxicities, weight loss has a later onset with vismodegib, with a reported median time to onset of 175 days
after initiation (35). Because of the late onset and the relatively short follow-up times in many clinical trials, the true incidence of weight loss may be underreported. For instance, in an expanded access study of vismodegib with a median exposure time of 5 months, approximately 20% of patients experienced grade 1 or 2 weight loss, whereas in a phase 2 study with median exposure time of 10 months, approximately 46% of patients experienced grade 1 to 4 weight loss (Table 2) (16, 35). Similarly, a phase 2 study of sonidegib showed that 27% of patients receiving the 200-mg once-daily dosage experienced weight loss (Table 2) (12, 13).

Management of weight loss depends on the severity of the side effect. For moderate to severe weight loss, high calorie nutritional supplements and consultation with an oncologic nutritionist may be of benefit. In our patients, oral megestrol acetate or dronabinol has helped to stimulate appetite but formal studies are needed to determine the optimal strategies to combat or reduce the weight loss side effect.

Discussion

Because the SI drug class is new, long-term data on AEs and their management are forthcoming. Studies directed at managing side effects are underway and more are needed. Multidisciplinary care to manage toxicities, including regular skin cancer surveillance by a dermatologist, is crucial. Given the potential long-term nature of SI treatment, with responsive metastatic BCC patients dosed indefinitely until tumor progression, the ability to successfully manage side effects is critical for patient adherence and quality of life.

Acknowledgments

The authors thank Christopher Reina, PhD, and Jillian Brechbiel, PhD, of Articulate Science, LLC, for medical editorial assistance with this manuscript. Financial support for editorial assistance was provided by Novartis Pharmaceuticals Corporation.
References


12. Migden MR, Guminski AD, Gutzmer R, Dirix LY, Lewis KD, Combemale P, et al. Randomized, double-blind study of sonidegib (LDE225) in patients (pts) with locally advanced...
(la) or metastatic (m) basal-cell carcinoma (BCC). J Clin Oncol 32:5s, 2014 [suppl; abstr 9009a].


34. Erivedge (vismodegib) prescribing information [PDF on the Internet]. San Francisco: Genentech; 2012 [cited 2015 Feb 19]. Available from:


Table 1. Cutaneous side effects of smoothened inhibitors organized by reported time to clinical onset. The side effect profile is pooled from published literature in human trials for smoothened inhibitors, including vismodegib (GDC0449), sonidegib (LDE225), saridegib (IPI-926), and BMS-833923 (XL139). Shaded rows indicate a side effect observed with more than 1 smoothened inhibitor.

<table>
<thead>
<tr>
<th>Observed Side Effect</th>
<th>Incidence</th>
<th>Average Time to Onset of Symptoms</th>
<th>Reported Severity (grade)</th>
<th>Reported or Hypothesized Mechanism</th>
<th>Management Options (level IV evidence)</th>
<th>Selected References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair loss</td>
<td>Vismodegib: 58%-63%&lt;sup&gt;b&lt;/sup&gt; Sonidegib: 16.7%-43%&lt;sup&gt;c&lt;/sup&gt; Saridegib: 22%&lt;sup&gt;d&lt;/sup&gt; BMS-833923: 15%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-4 months&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1/2&lt;sup&gt;b&lt;/sup&gt; 3/4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Inhibition of hair follicle regeneration (Rittie et al [2009], Chiang et al [1999])</td>
<td>No known effective treatment to date, reversible after discontinuation</td>
<td>Vismodegib: Sekulic et al., 2012 (16) Dirix et al., 2012 (43) Chang et al., 2014 (35) Sonidegib: Migden et al., 2014 (12), Dummer et al., 2014 (13), Rodon et al., 2014 (15) Saridegib: Jimeno et al., 2013 (14) BMS-833923: Siu et al., 2010 (17)</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>Unknown</td>
<td>3 weeks-8 months</td>
<td>1/2</td>
<td>Not well characterized</td>
<td>Antihistamines, topical steroids</td>
<td>Vismodegib: Lam et al., 2014 (41) Kwong et al., 2014 (42)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Vismodegib: 11%</td>
<td>1 month-8 years</td>
<td>3</td>
<td>Unclear if advanced BCC patients have increased risk of SCC versus detection bias from increased monitoring while receiving smoothened inhibitors versus smoothened inhibitor drug effect. In a mouse model, a particular Ptch1 mutation can lead to Ras activation with SCC formation, independent of</td>
<td>Excision, regular full-body skin examination for surveillance</td>
<td>Vismodegib: Iarrobino et al., 2013 (37) Orouji et al., 2014 (38) Saints et al., 2014 (39) Zhu et al., 2014 (40) Sekulic et al., 2014 (32) Mouse model of SCC formation via Ptch1 mutation: Wakabayashi et al., 2007 (58)</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>Not well characterized</td>
<td>2-7 weeks</td>
<td>3</td>
<td>Promotion of squamous differentiation</td>
<td>Surgical excision and regular full body skin checks</td>
<td>Vismodegib: Aasi et al., 2013 (36)</td>
</tr>
</tbody>
</table>

a Levels of evidence: level II: prospective comparative studies, systematic review of level II studies or level I studies with inconsistent results; level III: case-control studies, retrospective comparative studies, systematic review of level III studies; level IV: case series with no comparison group, retrospective case series.

b Vismodegib at 150-mg daily dose.
c Sonidegib at 200-mg daily dose.
d Saridegib at 160-mg daily dose.
e BMS-833923 based on phase 1 study of 28 patients at 30-540 mg daily, as AE rates at individual doses not provided.
f Based on a phase 2 study of vismodegib (35).
Table 2. Extracutaneous side effects of smoothened inhibitors organized by reported time to clinical onset. The side effect profile is pooled from published literature in human trials for smoothened inhibitors, including vismodegib (GDC0449), sonidegib (LDE225), saridegib (IPI-926), and BMS-833923 (XL139). Shaded rows indicate a side effect observed with more than 1 smoothened inhibitor.

<table>
<thead>
<tr>
<th>Observed Side Effect</th>
<th>Incidence</th>
<th>Average Time to Onset of Symptoms</th>
<th>Reported Severity (grade)</th>
<th>Reported Mechanism</th>
<th>Management Options (level IV evidence)</th>
<th>Selected References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Vismodegib: 19.3%-29% Sonidegib: 16.7%-33% Saridegib: 33% BMS-833923: 11%</td>
<td>1 week-4 months(^f)</td>
<td>1/2(^b), 3/4(^b,c)</td>
<td>Impaired GI motility</td>
<td>Antiemetic (e.g., ondansetron), appetite stimulant (e.g., megestrol, dronabinol), H2 antagonists</td>
<td>Vismodegib: Sekulic et al., 2012 (16) Chang et al., 2014 (35) Sonidegib: Migden et al., 2014 (12) Dummer et al., 2014 (13) Rodon et al., 2014 (15) Saridegib: Jimeno et al., 2013 (14) BMS-833923: Siu et al., 2010 (17)</td>
</tr>
<tr>
<td>Amenorrhea or irregular menses</td>
<td>Vismodegib: Up to 50%(^b)</td>
<td>1 month</td>
<td>1</td>
<td>Mechanism unclear, could be target effects on uterus</td>
<td>May resolve upon discontinuation of vismodegib</td>
<td>Vismodegib: Chang et al., 2014 (35) Strasswimmer et al., 2014 (46)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Vismodegib: 51%-70.6% Sonidegib: 16.7%-38% Saridegib: 27.8% BMS-833923: 44%</td>
<td>1-2 months(^f)</td>
<td>1/2(^b,c,d,e), 3/4(^d)</td>
<td>Inhibition of lingual papillae development in animal model (Liu et al [2004] and Castillo et al [2014])</td>
<td>Supportive care (e.g., strongly flavored food, baking soda mouth rinse, etc.)(^f)</td>
<td>Vismodegib: Sekulic et al., 2012 (16) Chang et al., 2014 (35) Sonidegib: Migden et al., 2014 (12) Dummer et al., 2014 (13) Rodon et al., 2014 (15) Saridegib: Jimeno et al., 2013 (14) BMS-833923: Siu et al., 2010 (17)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>Vismodegib: 68%-70.6% Sonidegib: 33.3%-50% Saridegib: 33% BMS-833923: 44%</td>
<td>1-2 months(^f)</td>
<td>1/2(^b,c,d,e), 3/4(^b,c)</td>
<td>Inhibition of muscle repair in animal model (Li et al [2004], Straface et al [2009], Piccioni et al [2014])</td>
<td>Muscle relaxant (e.g., cyclobenzaprine), levocarnitine(^g)</td>
<td>Vismodegib: Sekulic et al., 2012 (16) Chang et al., 2014 (35) Sonidegib: Migden et al., 2014 (12) Dummer et al., 2014 (13) Rodon et al., 2014 (15)</td>
</tr>
<tr>
<td>Condition</td>
<td>Agent</td>
<td>Incidence</td>
<td>Duration</td>
<td>Level of Evidence</td>
<td>Additional Information</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>----------</td>
<td>------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Elevated creatine kinase&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sonidegib: 16.7%-29%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6-8 weeks</td>
<td>2-4</td>
<td>2</td>
<td>Inhibition of Hh-regulated skeletal muscle repair Monitor for rhabdomyolysis, avoid overexertion and concomitant medications that may exacerbate</td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Vismodegib: 1%-26.5%&lt;sup&gt;a&lt;/sup&gt; Saridegib: up to 88.9%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1-3 months</td>
<td>2-4</td>
<td>3</td>
<td>Drug-drug interaction, direct hepatocellular damage, impaired hepatocyte regeneration Consider removing any interacting concomitant medications</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Vismodegib: 16%-46%&lt;sup&gt;b&lt;/sup&gt; Saridegib: 16.7%-27%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-10 months&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1/2&lt;sup&gt;b,c&lt;/sup&gt; 3/4&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>4</td>
<td>Likely multifactorial, including decreased dietary intake due to GI side effects Appetite stimulant, calorie-dense dietary supplements</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Levels of evidence: level II: prospective comparative studies, systematic review of level II studies or level I studies with inconsistent results; level III: case-control studies, retrospective comparative studies, systematic review of level III studies; level IV: case series with no comparison group, retrospective case series.

<sup>b</sup>Vismodegib at 150-mg daily dose.

<sup>c</sup>Saridegib at 200-mg daily dose.

<sup>d</sup>Saridegib at 160-mg daily dose.

<sup>e</sup>BMS-833923 based on phase 1 study of 28 patients at 30 to 540 mg daily, as AE rates at individual doses not provided.

<sup>f</sup>Based on McNabb, 2013 (51).

<sup>g</sup>L-carnitine benefit is currently being evaluated in a clinical trial (NCT01893892).

<sup>h</sup>Based on a phase 2 study of vismodegib (35).
Clinical Cancer Research

Management of Cutaneous and Extracutaneous Side Effects of Smoothened Inhibitor Therapy for Advanced Basal Cell Carcinoma

Shalini V Mohan and Anne Lynn S Chang

Clin Cancer Res  Published OnlineFirst March 19, 2015.

Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-14-3180

Author Manuscript  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pub@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.