



Sonidegib (Odomzo) for the Systemic Treatment of Adults With Recurrent, Locally Advanced Basal Cell Skin Cancer

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INTRODUCTION

Non-melanoma skin cancer (NMSC) is the most common malignancy in the United States, with more than 5.4 million cases diagnosed annually.¹ NMSC is categorized as either basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), with BCC occurring at a fourfold to fivefold higher rate than SCC. Standard first-line treatment of BCC usually involves local procedures, such as curettage, electrodesiccation, surgical excision, or radiation therapy.² In the most recent data (from 2011), total health care expenditures for cancer treatments in the U.S. were estimated to exceed \$88 billion, including \$4.8 billion for NMSC.^{3,4} While the cost of treating NMSC may be a small fraction of the overall cost of cancer therapies, additional factors must be considered. For instance, the rate of BCC is expected to grow as specific populations expand, such as people older than 65 years of age, immunosuppressed patients, and previously treated patients experiencing disease recurrence; this may increase costs.⁵

Estimates of the rate of locally advanced BCC (laBCC) or metastatic BCC (mBCC) are elusive because of a lack of standardization in staging and reporting requirements, but it has been estimated that laBCC occurs in 1% to 10% of BCC patients, and that mBCC occurs in 0.0028% to 0.5% of BCC patients.⁶ Patients with mBCC have a median survival of eight months.⁷ Until recently, only limited treatment options,

such as cisplatin, have been available for patients with laBCC or mBCC⁸; however, the discovery of the key role played by the hedgehog (Hh) signaling pathway in tumorigenesis has opened the door for the development of new therapies, such as vismodegib (Erivedge, Genentech).⁹

Smoothed (SMO), a transmembrane protein, activates the Hh pathway, leading to the production of glioma-associated oncogene transcription factors (GLI1, GLI2, and GLI3). These factors are the final component of the pathway that regulates cellular differentiation, proliferation, and survival.¹⁰

In July 2015, the Food and Drug Administration (FDA) approved the SMO inhibitor sonidegib (Odomzo, Novartis) for the treatment of adults with laBCC that has recurred after surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.^{11,12} Sonidegib's key competitor is vismodegib, another SMO inhibitor, which has been used since 2012 to treat patients with laBCC who are not candidates for surgery or radiation and patients with mBCC.^{13,14} Vismodegib was the first FDA-approved drug for advanced BCC.¹³

MECHANISM OF ACTION

Sonidegib is an inhibitor of the Hh pathway, binding to and inhibiting SMO. It has demonstrated a variety of effects on tumor cells, including reduced cell viability, reduced GLI homolog activity, and enhanced apoptosis.¹²

Sonidegib's chemical structure is shown in Figure 1.

PHARMACOKINETICS¹²

Less than 10% of an oral dose of sonidegib is absorbed. After the administration of a single dose (100 mg to 3,000 mg) under fasted conditions in patients with cancer, the median time to peak concentration was two to four hours. Steady state was reached approximately four months after starting sonidegib. After a dose of 200 mg once daily, the estimated mean steady-state maximum concentration was 1,030 ng/mL; the area under the curve was 22 mcg•h/mL; and the minimal concentration was 890 ng/mL. A high-fat meal (approximately 1,000 calories, with 50% of calories from fat) increased exposure to sonidegib by 7.4- to 7.8-fold.

The estimated apparent steady-state volume of distribution for sonidegib is 9,166 L. Sonidegib was highly bound (greater than 97%) to human plasma proteins *in vitro*, and this binding was concentration independent. *In vitro* studies have suggested that sonidegib is not a substrate of ABCB1 (P-glycoprotein), ABCC2 (MRP2, cMOAT), or ABCG2 (BCRP).

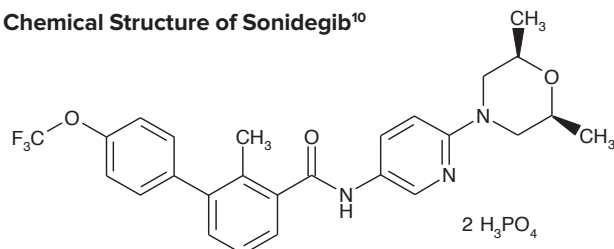
The elimination half-life of sonidegib is approximately 28 days. Sonidegib is primarily metabolized by cytochrome P450 (CYP) 3A. The main circulating compound is unchanged sonidegib.

Sonidegib and its metabolites are eliminated primarily by the hepatic route. Of the absorbed dose, approximately 70% is eliminated in the feces and 30% is eliminated in the urine. Unchanged sonidegib was not detectable in urine.

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Figure 1 Chemical Structure of Sonidegib¹⁰



CLINICAL TRIALS

Phase 1 Study¹⁶

A phase 1, open-label, dose-escalation study was conducted to determine the maximum tolerated dose and dose-limiting toxicities of sonidegib in patients with various solid tumors. In addition, the patients were monitored for safety, antitumor activity, pharmacokinetics, and pharmacodynamics. The subjects received doses ranging from 100 mg to 3,000 mg once daily and from 250 mg to 750 mg twice daily in a 28-day cycle.

A total of 103 patients were enrolled—73 in the once-daily groups and 30 in the twice-daily groups. The patients' median age was 59 years (range, 22–87 years). Most of the patients were male, had received extensive prior therapies for their cancer, and had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

Sixteen patients had laBCC or mBCC. Of these patients, six (37.5%) achieved a partial or complete tumor response. The complete response occurred in a patient with laBCC after treatment with 400 mg twice daily. The most common adverse events included nausea, dysgeusia, muscle spasms, myalgia, and alopecia.

Pivotal Phase 2 Study¹⁷

The FDA approval of sonidegib for the treatment of patients with laBCC was based on results from a pivotal phase 2, randomized, double-blind trial involving a total of 230 patients who had laBCC that could not be treated with surgery or radiation or who had mBCC. The patients were randomly assigned to receive either 200 mg or 800 mg of oral sonidegib once daily until disease progression or intolerable toxicity occurred. The study's primary endpoint was the proportion of patients who achieved an objective response (OR), as determined by modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC or by RECIST version 1.1 for patients with mBCC.

Sixty-six patients with laBCC and 13 patients with mBCC were treated with sonidegib 200 mg once daily. The patients' median age was 67 years (range, 25–92 years); 58% were male; and 89% were white. Most of the patients (67%) had an ECOG performance status of 0, and 56% had aggressive histology. Seventy-six percent of the patients had

received prior therapy for BCC, including surgery (73%), radiotherapy (18%), or topical or photodynamic treatments (21%). The group treated with sonidegib 800 mg once daily consisted of 128 patients with laBCC and 23 patients with mBCC. The demographic characteristics of these patients were similar to those of the 200-mg group.

The patients with laBCC in the sonidegib 200-mg group were followed for at least 12 months unless they discontinued treatment earlier. The primary endpoint of OR was reached in 58% of these patients, who showed three complete responses and 35 partial responses. The patients with laBCC who received sonidegib 800 mg once daily had an OR rate of 45%, indicating that the higher dose did not provide better antitumor activity than the lower dose in this cohort.

SAFETY PROFILE

Adverse Events

The pivotal safety data for sonidegib were derived from the phase 2 study described above, in which 79 patients with laBCC (n = 66) or mBCC (n = 13) were treated with sonidegib 200 mg once daily.^{12,17} The most common adverse events (AEs) of any grade in this cohort included muscle spasms (54%), alopecia (53%), dysgeusia (46%), fatigue (41%), nausea (39%), musculoskeletal pain (32%), diarrhea (32%), decreased weight (30%), decreased appetite (23%), and myalgia (19%). The most common grade-3 AEs included fatigue (4%), muscle spasms (3%), decreased weight (3%), musculoskeletal pain, headache, nausea, diarrhea, vomiting, and decreased appetite (each 1%).^{12,17}

Warnings and Precautions¹²

Embryo-Fetal Toxicity

The labeling for sonidegib includes a boxed warning regarding the potential for embryo-fetal toxicity. Sonidegib can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is embryotoxic, fetotoxic, and teratogenic in animals. Clinicians should verify the pregnancy status of women of reproductive potential before initiating therapy. They should also advise women of reproductive potential to use effective contraception during treatment with sonidegib and for at least 20 months after the last dose. Moreover, men should be made aware of the potential risk of expo-

sure through semen and the need to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with sonidegib and for at least eight months after the last dose. Patients receiving sonidegib should not donate blood or blood products for at least 20 months after the last dose because their blood or blood products might be given to women of reproductive potential.

Musculoskeletal Adverse Events

Musculoskeletal AEs, which may be accompanied by serum creatine kinase (CK) elevations, can occur during treatment with drugs that inhibit the Hh pathway, including sonidegib. In the pivotal phase 2 study of sonidegib, musculoskeletal AEs occurred in 68% (54/79) of patients treated with sonidegib 200 mg daily, with 9% (7/79) reported as grade 3 or 4. The most common musculoskeletal AEs included muscle spasms (54%), musculoskeletal pain (32%), and myalgia (19%). Increased serum CK laboratory values occurred in 61% (48/79) of patients, with 8% (6/79) of patients having grade 3 or 4 serum CK elevations. Musculoskeletal pain and myalgia usually preceded serum CK elevations.

Use in Specific Populations¹²

Pregnancy and Lactation

No clinical data are available on the use of sonidegib in pregnant women. Based on the drug's mechanism of action and data from animal reproduction studies, sonidegib can cause fetal harm when given to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus.

No data are available regarding the presence of sonidegib in human milk. Because of the potential for serious AEs in breastfed infants, clinicians should advise nursing women not to breastfeed during treatment with sonidegib and for 20 months after the last dose.

Geriatric and Pediatric Use

In the pivotal phase 2 study of sonidegib, 229 patients were evaluable for safety. Of these subjects, 54% were 65 years of age or older, whereas 28% were 75 years of age or older. No overall differences in efficacy were observed between these patients and younger patients. More grade-3 and -4 AEs, as well as more AEs requiring dose interrup-

Table 1 Comparison of Objective Response Rates Between Smoothened Inhibitors

	Sonidegib ^{17,a}		Vismodegib ^{20,b}	
	laBCC, n = 66	mBCC, n = 13	laBCC, n = 63	mBCC, n = 33
Objective response rate	31 (47%)	2 (15%)	27 (43%)	10 (30%)
Partial response	29 (44%)	2 (15%)	13 (21%)	14 (22%)
Complete response	2 (3%)	0 (0%)	13 (21%)	0 (0%)
Median duration of response (months)	Not reached ^c		7.6 (95% CI, 5.7–9.7)	

CI = confidence interval; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma.

^a Objective response rate determined by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for laBCC and RECIST v1.1 for mBCC in a randomized, double-blind trial. Participants (median age, approximately 66; 94% white; 63% male) received 200 mg or 800 mg of sonidegib with a median follow-up of 13.9 months.¹⁵

^b Objective response rate in laBCC was defined as a decrease of 30% or more in the externally visible or radiographic dimension (if applicable) or complete resolution of ulceration (if present at baseline) and mBCC by RECIST v1.0. Data were collected over 21.6 months in a nonrandomized trial; all participants (median age, 62; 100% white; 61% male) received 150 mg of oral vismodegib daily.¹⁷

^c Some patients continued to respond up to 18.1 months into therapy.

tion or discontinuation, were observed in patients 65 years of age or older compared with younger patients.

The safety and efficacy of sonidegib have not been established in pediatric patients.

Hepatic and Renal Impairment

No dose adjustments are recommended for patients with mild hepatic impairment or any degree of renal impairment. Sonidegib has not been studied in patients with moderate or severe hepatic impairment.

Drug–Drug Interactions¹²

The concomitant administration of sonidegib with strong or moderate CYP3A inhibitors should be avoided. Strong inhibitors include saquinavir, telithromycin, and ketoconazole, and moderate inhibitors include atanzavir, diltiazem, and fluconazole. If a moderate CYP3A inhibitor must be used, it should be administered for less than 14 days, and the patient should be monitored closely for AEs, particularly musculoskeletal AEs.

Clinicians should also avoid the concomitant use of sonidegib with strong or moderate CYP3A inducers, including carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort.

DOSAGE AND ADMINISTRATION

The recommended dosage of sonidegib is 200 mg once daily, taken on an empty stomach at least one hour before or two hours after a meal. The drug is administered until disease progression or unacceptable toxicity occurs.¹²

COST

Sonidegib is packaged as 200-mg capsules in a 30-count bottle, which has an average wholesale price (AWP) of \$12,072. This corresponds to \$146,876 per year.¹⁸ The AWP for vismodegib, the other approved Hh inhibitor, is comparable at \$11,832 for a 28-count bottle of 150-mg capsules, totaling \$154,242 per year.¹⁶ Novartis offers a program to provide reimbursement options for patients who cannot afford sonidegib.¹⁹

P&T COMMITTEE CONSIDERATIONS

The current National Comprehensive Cancer Network (NCCN) treatment guidelines for patients with BCC—published before sonidegib was approved—recommend vismodegib as an option for patients with advanced disease who have exhausted surgical and radiation options.² Sonidegib shares the same mechanism of action and the same indication for locally advanced disease.^{12,14}

As noted previously, sonidegib and vismodegib both inhibit the Hh pathway by binding to and inhibiting SMO, and both are indicated for the treatment of patients with laBCC. Vismodegib has the additional indication of mBCC. Although both treatments are administered once daily, high-fat meals increase the exposure of sonidegib, whereas vismodegib may be given without regard to meals. Both drugs are linked to embryo-fetal toxicity.^{12,14} Finally, with regard to cost, sonidegib has a marginally lower AWP compared with vismodegib (\$12,072 for a 30-day supply versus \$12,677, respectively).¹⁸

A comparison of the objective response rates between sonidegib and vismodegib based on comparative phase 3 trial data in patients with laBCC and mBCC is provided in Table 1.^{17,20}

CONCLUSION

The Hh pathway inhibitor sonidegib, approved in July 2015, offers a promising new option for the treatment of patients with laBCC that has recurred after surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.¹² Its chief competitor is another Hh pathway inhibitor, vismodegib—the first drug approved for the treatment of advanced BCC.¹⁴

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