

# Differential pharmacology and clinical utility of sonidegib in advanced basal cell carcinoma

Mohd Wahid  
Arshad Jawed  
Sajad Ahmad Dar  
Raju K Mandal  
Shafiul Haque

Research and Scientific Studies Unit,  
College of Nursing and Allied Health  
Sciences, Jazan University, Jazan,  
Kingdom of Saudi Arabia

**Abstract:** Patients suffering from advanced basal cell carcinoma (BCC) have very limited treatment options. Sonidegib selectively inhibits the growth of Hedgehog pathway-dependent tumors and can treat locally advanced BCC patients who are not candidates for surgery or radiation therapy. The BOLT clinical trials were conducted to evaluate the efficacy/potency of sonidegib in the treatment of advanced BCC or metastatic BCC. The patients were randomized in 1:2 ratios to receive 200 or 800 mg oral sonidegib daily, stratified by disease, histological subtype and geographical region. The primary efficacy analyses showed that 18 patients in the 200 mg group and 35 patients in the 800 mg group show an objective response (Central Review Committee) that corresponds to 43% (95% confidence interval [CI]: 28–59) and 38% (95% CI: 28–48) in their respective categories. Disease control was found in 93% (39 patients) and 80% (74 patients) of the patients administered 200 and 800 mg sonidegib, respectively. The adverse events were assessed by the Central Review Committee as well as the investigator review team as per the guidelines of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The most frequently found adverse events reported in BOLT trials were muscle spasms, alopecia, dysgeusia (taste disturbance), nausea, elevated blood creatine kinase and fatigue. Comparatively, the patients administered 200 mg sonidegib showed fewer adverse events than those in the 800 mg sonidegib category. Thus, the benefit of using the 200 mg dose of sonidegib outweighs the associated risks and it can be inferred that it would be judicious to choose doses of lesser strength.

**Keywords:** locally advanced basal cell carcinoma, metastatic basal cell carcinoma, central review, investigator review, BOLT clinical trials, objective response, complete response, partial response, disease control, event-free probability

## Introduction

The history of oncology treatment has been associated with pessimism. The outcome of treatment becomes more uncertain for advanced basal cell carcinomas (BCCs). A majority of the BCCs are simple, but they pose a colossal challenge on reaching an advanced/metastatic stage.<sup>1</sup> It is the most common malignancy responsible for human skin cancer, accounting for almost 80% cases.<sup>2,3</sup> Sonidegib (Odomzo<sup>®</sup>, Novartis International AG, Basel, Switzerland) appeared as a ray of hope for advanced BCC-affected patients because of a satisfactory benefit–risk profile and the shortage of treatments available for this disease.<sup>4</sup> Sonidegib is an oral Smoothened (SMO) antagonist, which acts as a Hedgehog pathway inhibitor. It is indicated for the treatment of adults with locally advanced BCC (laBCC) not suitable for surgery or radiation therapy or adults with recurrent laBCC following surgery or radiation therapy.<sup>4</sup>

Correspondence: Shafiul Haque  
Research and Scientific Studies Unit,  
College of Nursing and Allied Health  
Sciences, Jazan University, Jazan 45142,  
Kingdom of Saudi Arabia  
Tel/fax +966 17 317 4383  
Email shafiul.haque@hotmail.com

## Treatment management of advanced BCC

The incidence of BCCs is increasing by leaps and bounds across nations, particularly in the United States. Thus, scientists working all over the world have focused their attention on finding a successful treatment for advanced BCCs.<sup>5</sup> The aim of the BCC treatment is to remove the tumor without much alteration in the function or physical appearance of the patient's affected area. The features that make advanced BCCs difficult to treat are large tumor size, location, extent and invasiveness of the disease.<sup>6</sup> Different treatment options for advanced BCCs, such as electrodesiccation, curettage, cryosurgery, photodynamic therapy or topical agents, did not get the expected success. If there exists the possibility of surgery without deformity or loss of function to the patient for the treatment of advanced BCC, it is considered one of the best options.<sup>7</sup>

Radiation therapy has also been used for a long time to treat advanced BCCs and various other tumors. It utilizes high-energy rays, eg, X-rays, and particles, such as photons, electrons or protons, to kill tumor cells. This treatment is particularly useful when the tumor size is very large or on areas where surgical removal is difficult. It is also useful for patients who cannot withstand surgery due to other health reasons such as diabetes, old age, etc.<sup>8</sup>

The new category of drugs surfacing currently comprises oral agents that act as Hedgehog pathway inhibitors and that are very beneficial for the treatment of advanced BCC. The first-in-class drug in this category was vismodegib (Erivedge; Genentech, Inc., South San Francisco, CA, USA), made by Genentech, which received US Food and Drug Administration (FDA) approval and European marketing authorization the year 2012 and 2013, respectively.<sup>9</sup> A new drug making waves these days, named sonidegib, has also been added in this category.

## Challenges faced by Hedgehog pathway inhibitors

The failure of cancer drugs to treat diseases after showing their credentials is becoming common nowadays. The drugs are not losing their strength because of any alteration in their structure or way of functioning. The reason is mainly the drug resistance that develops due to change in the drug target.<sup>10</sup> Drug resistance influences the treatment of various cancers such as blood cancer and solid tumors that include non-Hodgkin lymphoma, breast cancer, lung cancer and BCCs. The drugs such as vismodegib and sonidegib are also not left untouched by the problem of drug resistance.<sup>11</sup>

Vismodegib is affected by both primary and secondary resistances. The reason for primary resistance includes the mutation in SMO at position 497 (G→W) in patients, whereby tumors started to grow after 2 months of randomization with vismodegib. The second type of resistance developing in the case of vismodegib use was due to a nonsense mutation in PTCH1 after following 11 months' continuous treatment. The mutation in SMO was found to be at position 473 (D→Y).

The mutation that affects the treatment of advanced BCC by sonidegib is located at position 477 in SMO. This mutation at position 477 results in a change in amino acid from aspartic acid to glycine (D→G). This change leads to reduced sensitivity to Hedgehog pathway inhibitors and affects drug–target binding. The mentioned change is an acquired resistance that annuls the susceptibility of the advanced BCC patients to sonidegib treatment.<sup>12</sup> It is a potential hurdle to durable response in the clinics. Alternate approaches of combining the different Hedgehog pathway inhibitors together to overcome 1 or more resistance can provide extra strength to treatment regimens for advanced BCC.

## Vismodegib

Vismodegib inhibits the Hedgehog pathway by attaching itself to SMO (a transmembrane protein involved in Hedgehog pathway signal transduction). It is a first-in-class SMO inhibitor approved by the US FDA in January 2012. It was filed under priority review for the treatment of metastatic or advanced BCC, which appears again after surgery or is incurable with surgery or radiation due to significant deformity or loss of function.<sup>13</sup>

## Pharmacokinetics

Vismodegib is a very permeable compound with absolute bioavailability of 31.8%. The absorption rate of vismodegib reaches a saturable point after a single dose of 270 or 540 mg.<sup>13</sup>

The distribution of vismodegib varies from 16.4 to 26.6 L. The plasma protein binding of vismodegib is more than 99% and it binds to both human serum albumin and alpha-1-acid glycoprotein (saturable limit).

Vismodegib as a whole and its metabolites, are eliminated mainly by the hepatic route. Thus, 82% of the total administered dose is recovered in the feces, whereas 4.4% is recovered in urine. The  $t_{1/2}$  (half-life) of vismodegib as calculated was 4 days after continuous administration of once-daily dose and 12 days after a single dose.

## Efficacy of vismodegib

Vismodegib has shown good results in an international, 2-cohort phase 2 trial in patients suffering from metastatic BCC or laBCC, conducted in the year 2012. These trials were conducted to test the efficacy of the drug.<sup>1</sup> The number of patients suffering from laBCC was 71 out of 104 enrolled for the study. Eight patients were dropped from the study as they did not fulfill the criteria, such as histologically confirmed laBCC, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a skin lesion of not less than 10 mm (for locally advanced patients) and nonfeasibility of surgical or radiotherapeutic treatment. The remaining 63 patients suffering from laBCC were assessed by independent investigators. Objective response was shown by 27 patients, which corresponds to almost 43% (95% confidence interval [CI]: 31–56;  $P < 0.001$ ), with 21% patients (ie, 13 patients) showing complete response. Thus, vismodegib shows good efficacy in the treatment of laBCC.

## Sonidegib

Sonidegib, with the trade name Odomzo®, is a Hedgehog pathway inhibitor approved by the US FDA in the year 2015 for the treatment of patients suffering from laBCC that has recurred following surgery or radiation therapy or for those on whom surgery/radiation therapy cannot be performed. It binds Smo (a transmembrane protein), which results in the inhibition of Hedgehog signal transduction. It helps in reducing the growth of cancer cells. The recommended dose of sonidegib is 200 mg taken orally once a day on an empty stomach.<sup>14</sup> A majority of cancer treatments produce mild-to-moderate adverse events that can be managed with dosage modification, concomitant medications, adequate hydration, etc.

## Pharmacokinetics

Less than 10% is absorbed in the patient's body from the total administered dose. After the administration of a single oral dose (from 100 to 3,000 mg) of sonidegib under fasting conditions to patients suffering from cancer, it attains the median time to peak concentration ( $T_{max}$ ) in approximately 2–4 hours, whereas after repeated dosing,  $T_{max}$  is reached after 2–13 hours.<sup>15,16</sup> Sonidegib is mainly metabolized by the liver through the action of cytochrome P450 3A (CYP3A).<sup>13–15,17</sup> The estimated  $t_{1/2}$  of sonidegib as calculated using population pharmacokinetics (PKs) is approximately 28 days and it is mainly excreted out through the hepatic route. From the total absorbed dose of sonidegib, 70% is removed in the feces, whereas 30% is eliminated along with urine.<sup>16,18</sup>

## Efficacy of sonidegib

The potential of any drug is measured by assessing the maximum response achievable and capacity for sufficient therapeutic effect that benefits the patient/ultimate user. The therapeutic competence of any drug is proved first in clinical trials, followed by its launch in the market.

The evaluation of sonidegib's efficacy was done in a clinical trial named BOLT.<sup>19</sup> It was a multicenter, randomized, double-blind phase 2 study conducted in 58 centers across 12 countries.

### Patient selection method

Almost 269 patients were screened for inclusion in the clinical trials. The eligible patients had to fulfill the conditions such as age of the patients (18 years or more), histologically confirmed laBCC (disease not manageable by radiotherapy or curative surgery), or metastatic BCC for which the available treatments were not working. The patients had WHO status from 0 to 2.<sup>20</sup> All the patients had given their written consent before their enrollment in the clinical trials. The number of patients not enrolled in the study was 39. Out of these 39 patients, 30 did not qualify in the eligibility criteria, whereas 6 patients retracted by themselves and 3 patients were excluded by the physician. The remaining 230 patients were randomized and administered 2 doses of sonidegib daily in separate groups of 200 and 800 mg, until they had disease progression, incidence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent. The number of patients assigned for 200 and 800 mg doses were 79 and 151, respectively. The patients included in the primary efficacy analysis were 55 for the 200 mg dosage group, whereas for the 800 mg dosage group, the number was 116. Both 200 and 800 mg dosage groups included the patients for the safety analysis as well. All the patients in the 200 mg intent-to-treat population (ie, 79) were used for the safety analysis, whereas for the 800 mg category, the patients used for the safety analysis were 150 out of 151.

The primary efficacy analysis of sonidegib for the treatment of laBCC was divided into 2 categories, namely, administration of 200 and 800 mg sonidegib (Table 1). The first category of 42 patients was administered 200 mg of sonidegib daily, whereas the second category of 93 patients was infused with 800 mg of sonidegib once daily. The various end points analyzed were objective response, disease control, duration of tumor response, progression-free survival, etc. The study was assumed to be successful if 30% or more of the patients achieved objective response. The Central Review Committee,

**Table 1** Comparison of response rates of patients administered 200 and 800 mg sonidegib to evaluate its activity against laBCC in the primary efficacy and intent-to-treat populations

<b>Activity of sonidegib for the treatment of locally advanced basal cell carcinoma in the primary efficacy and intent-to-treat populations</b>				
<b>Parameter studied</b>	<b>Primary efficacy population (laBCC)</b>		<b>Intent-to-treat population (laBCC)</b>	
	<b>Sonidegib (200 mg); n=42</b>	<b>Sonidegib (800 mg); n=93</b>	<b>Sonidegib (200 mg); n=66</b>	<b>Sonidegib (800 mg); n=128</b>
<b>Central review</b>				
<b>Proportion of patients (objective response)</b>	18 (43%)	35 (38%)	31 (47%)	45 (35%)
<b>[95% CI]</b>	[28–59]	[28–48]	[35–60]	[27–44]
Complete response	2 (5%)	0	2 (3%)	0
Partial response	16 (38%)	35 (38%)	29 (44%)	45 (35%)
<b>Disease control</b>	39 (93%)	74 (80%)	60 (91%)	100 (78%)
<b>Time to tumor response, months (95% CI)</b>	3.9 (2.1–4.0)	3.7 (2.0–3.8)	3.9 (3.6–4.2)	3.7 (2.6–3.8)
<b>Duration of tumor response</b>				
Number of events	3	1	4	3
Event-free probability (after 9 months of randomization)	82% [44–95]	92% [56–99]	83% [54–94]	83% [54–94]
<b>[95% CI]</b>				
<b>Progression-free survival</b>				
Number of events	5	8	7	10
Duration (months)	NR	NR	NR	NR
Event-free probability (after 12 months of randomization)	84% [59–94]	83% [67–91]	84% [65–93]	86% [73–93]
<b>[95% CI]</b>				
<b>Investigator review</b>				
<b>Proportion of patients (objective response)</b>	28 (67%)	54 (58%)	43 (65%)	73 (57%)
<b>[95% CI]</b>	[50–80]	[48–68]	[52–76]	[48–66]
Complete response	3 (7%)	12 (13%)	5 (8%)	15 (12%)
Partial response	25 (60%)	42 (45%)	38 (58%)	58 (45%)
<b>Disease control</b>	39 (93%)	82 (88%)	59 (89%)	110 (86%)
<b>Time to tumor response, months (95% CI)</b>	1.9 (1.2–3.7)	1.8 (1.1–2.0)	1.9 (1.8–3.7)	1.9 (1.2–2.0)
<b>Duration of tumor response</b>				
Number of events	5	6	10	10
Event-free probability (after 9 months of randomization)	84% [58–95]	81% [58–92]	74% [52–87]	77% [59–88]
<b>[95% CI]</b>				
<b>Progression-free survival</b>				
Number of events	9	13	15	17
Duration (months)	22	NR	17	NR
Event-free probability (after 12 months of randomization)	74% [50–87]	70% [52–82]	69% [51–81]	71% [57–882]
<b>[95% CI]</b>				

**Abbreviations:** CI, confidence interval; laBCC, locally advanced basal cell carcinoma; NR, not recorded.

after analyzing the BOLT trials, found that 43% patients in the 200 mg category and 38% in the 800 mg category showed objective response. Complete response was shown by 5% patients administered 200 mg sonidegib, whereas no patients administered 800 mg drug showed complete response. Partial response was shown by approximately 38% in both the categories of patients, while disease control was shown by 93% and 80% patients in their respective groups (ie, 200 and 800 mg). The investigator review committee had also analyzed the results of the BOLT clinical trials. Objective response was found to be 67% and 58% in the patients in 200 and 800 mg groups, respectively. Patients in both the groups, ie, 7% patients in the 200 mg group and 13%

patients in the 800 mg group, showed complete response. The partial responses were 60% and 45%, respectively, in the mentioned categories. The disease control was also excellent, as analyzed by the investigator review committee, shown by around 93% and 88% patients in the 200 and 800 mg categories, respectively. The results shown by both the analytical groups (ie, central review and investigator review) in the intent-to-treat population were also comparable with those of the primary efficacy patient population.

## Safety

The adverse events were assessed by the central review as well as by the investigator review teams.<sup>19</sup> All the Z events

experienced by the patients following the administration of 200 and 800 mg doses of sonidegib were reviewed as per the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.<sup>21</sup> The adverse events were evaluated from Day 1, when the first dose of sonidegib was administered, until the last dose, which was administered on Day 30. Generally, the most common adverse events reported in BOLT trials were muscle spasms, alopecia, dysgeusia (taste disturbance), nausea, elevated blood creatine kinase and fatigue.<sup>19</sup> The patient group administered 800 mg sonidegib showed adverse events more frequently compared with the patients infused with 200 mg of sonidegib. The most frequently reported grade 3–4 adverse events, such as elevated kinase levels, were shown by many patients, followed by increased lipase levels. If we consider both 200 and 800 mg sonidegib doses that were administered to both types of patients, those suffering from laBCC and metastatic BCC, the most common adverse event that led to the discontinuation of the treatment by the patients was muscle spasm (3/79 patients in the 200 mg sonidegib group and 13/150 patients in the 800 mg sonidegib group).

## Opinion

The Hedgehog inhibitors have proved themselves as promising alternatives for patients with advanced BCC who are not amenable to radiotherapy or surgery.<sup>22</sup> The current review is based mainly on BOLT clinical trials conducted across 12 countries all over the world in around 58 centers. It was a double-blind, randomized, phase 2 study to test the efficacy of sonidegib in 2 tolerable doses (ie, 200 and 800 mg) for the treatment of laBCC as well as metastatic BCC. The focus here is on laBCC, which affects many patients across the globe. The patients were analyzed and were assigned to laBCC and metastatic BCC groups as required. The laBCC patients (42 in number) were administered 200 mg sonidegib daily, whereas 93 patients were administered 800 mg sonidegib daily. The percentage of patients who showed objective response was 43% and 38% in their respective categories, which appears to be comparatively good, although complete response was shown by proportionately fewer patients in the 200 mg category and none in the 800 mg category. However, the disease control ratio was quite impressive, ie, 93% and 80%.

The safety profiles of both 200 and 800 mg sonidegib dosage groups were assessed by following the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.<sup>21</sup> The frequently found adverse events in the patients were muscle spasms, alopecia,

dysgeusia (taste disturbance), nausea, elevated blood creatine kinase and fatigue, which sometimes have led many patients to discontinue their treatment. These adverse reactions were more common in the patients administered 800 mg sonidegib. Drugs such as tizanidine (muscle relaxant) can be recommended to increase the tolerability of patients who show muscle toxicity after the administration of sonidegib. Furthermore, it was found in the study that muscle toxicity and dysgeusia were prominent between the first and third weeks. Hence, drug scheduling and reduced drug strength are recommended.<sup>23</sup>

The emergence or rebound of resistance in the case of vismodegib has already terrified other Hedgehog inhibitors as well.<sup>24</sup> Patients who were resistant to vismodegib for the treatment of advanced BCCs have continued the legacy for sonidegib.<sup>25</sup> So, alternate approaches of combining the drugs after assessing the mechanism of resistance developed in the laBCC patients are recommended, which would bypass the hindrance posed in the way of treating this category of patients. The combination of B-cell lymphoma-2 (BCL-2) inhibitors and chemotherapy has already shown promising results in overcoming acquired resistance.<sup>26,27</sup> The combination of BCL-2 inhibitors and chemotherapy sensitizes the resistant patients for cancer treatment. These BCL-2 inhibitors, if combined with sonidegib, may show better results and avoid advanced BCC recurrence due to acquired resistance.

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## Disclosure

The authors report no conflicts of interest in this work.

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