doi:10.36849/JDD.2021.5657

A Review of Hedgehog Inhibitors Sonidegib and Vismodegib for Treatment of Advanced Basal Cell Carcinoma

Michael Migden MD,[a] Aaron S. Farberg MD,[b] Reinhard Dummer MD,[c] Nicholas Squittieri MD,[d] C. William Hanke MD[e]

[a]Departments of Dermatology and Head and Neck Surgery, The University of Texas–MD Anderson Cancer Center, Houston, TX
[b]Section of Dermatology, Baylor University Medical Center, Dallas, TX
[c]Department of Dermatology, University of Zürich, Skin Cancer Center, University Hospital, Zürich, Switzerland
[d]Sun Pharmaceutical Industries, Inc., Princeton, NJ
[e]Ascension Saint Vincent Hospital, Indianapolis, IN

ABSTRACT

Basal cell carcinoma (BCC) is the most common malignancy in fair-skinned populations. Most cases are successfully treated with surgery, but in advanced BCC—including locally advanced BCC and metastatic BCC—surgery is likely to result in substantial morbidity or unlikely to be effective. In those patients, the systemic Hedgehog inhibitors (HHIs) sonidegib and vismodegib are the only approved pharmacologic treatment option. Although a number of clinical studies highlight the similarities and differences between the two HHIs, no head-to-head clinical comparison is available. Results from the pivotal BOLT and ERIVANCE clinical studies for sonidegib and vismodegib, respectively, demonstrate similar efficacy measured by objective response rate, complete response rate, and histologic tumor subtype. Safety results for both studies are comparable with similar common adverse events reported for muscle spasms, alopecia, and dysgeusia. A notable difference between sonidegib and vismodegib is their respective pharmacokinetic profiles with sonidegib reaching peak concentration in plasma within 2–4 hours of dosing and steady state in plasma achieved by week 17 of treatment, while vismodegib reaches peak plasma concentration approximately 2 days after a single dose and steady state within 21 days of repeated dosing. This review compares efficacy, safety, and pharmacokinetics of sonidegib and vismodegib based on published literature to date.

J Drugs Dermatol. 2021;20(2):156-165. doi:10.36849/JDD.2021.5657

INTRODUCTION

For the majority of basal cell carcinomas (BCCs), surgery is the standard of treatment with an excellent prognosis, as recommended by the American Academy of Dermatology and the European consensus-based interdisciplinary guidelines.[1,2] When surgery is contraindicated or unlikely to be effective, as in cases of locally advanced BCC (laBCC) or metastatic BCC (mBCC), systemic Hedgehog inhibitors (HHIs) are recommended.[1-3]

Two inhibitors of Smoothened, a Hedgehog pathway protein, are currently approved for treatment of advanced BCC. Sonidegib (Odomzo®; Sun Pharmaceutical Industries, Inc.; Cranbury, NJ) is approved in the US for the treatment of adults with laBCC that has recurred following surgery or radiation therapy, or for patients who are not candidates for surgery or radiation therapy.[4] In the EU, Switzerland, and Australia, sonidegib is approved for the treatment of adults with laBCC who are not amenable to curative surgery or radiation therapy.[5-7] Sonidegib is also indicated for mBCC in Switzerland and Australia.[6,7] Vismodegib (Erivedge®; Genentech, Inc.; San Francisco, CA) is approved in the US for the treatment of adults with mBCC, or laBCC that has recurred after surgery, or for those who are not candidates for surgery or radiotherapy.[8] In the EU, Switzerland, and Australia, it is indicated for adults with mBCC or laBCC inappropriate for surgery or radiotherapy.[9,10] In the absence of head-to-head clinical studies, this review summarizes and juxtaposes published reports to date on the efficacy, safety, and pharmacokinetics (PK) of sonidegib and vismodegib.

METHODOLOGY OF MAJOR CLINICAL STUDIES

Pivotal Studies in Advanced Basal Cell Carcinoma

The pivotal studies evaluating efficacy and safety of sonidegib and vismodegib in advanced BCC were BOLT (**B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment) for sonidegib, and ERIVANCE-BCC for vismodegib (Table 1). BOLT was a phase 2, randomized, double-blind, multicenter, adaptive clinical study, while ERIVANCE was a phase 2, single-arm, 2-cohort clinical study.[11,12]

Eligibility Criteria

Eligible patients in BOLT were ≥18 years old with an Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2.

TABLE 1.

Methodology of Major Studies Examining Efficacy and Safety of Sonidegib and Vismodegib

	BOLT sonidegib	ERIVANCE vismodegib	STEVIE vismodegib	MIKIE vismodegib
Study type	• Phase 2, randomized, double-blind, multicenter, adaptive	• Phase 2, single-arm, 2-cohort, multicenter	• Phase 2, single-arm, open-label, multicenter	• Phase 2, randomized, double-blind, regimen-controlled, multicenter
Analyses	• Primary at 6 months • Interim at 12, 18, and 30 months • Final at 42 months	• Primary at 9 months • Interim at 12 months • Final at 39 months	• Primary at median follow-up of 17.9 months	• Final at 124 weeks
Eligibility criteria	Inclusion criteria: • Age ≥18 years • ECOG status ≤2 • For laBCC: histologically confirmed diagnosis, tumor not amenable to surgery or radiotherapy, ≥1 lesion ≥10 mm in at least 1 dimension via MRI or color photography • For mBCC: all available treatments exhausted; ≥1 non-nodal lesion ≥2X slice thickness or 10 mm, measurable in ≥1 dimension by spiral CT or MRI, or 1 nodal lesion ≥15 mm in short axis by spiral CT or MRI • Bone marrow function assessments: absolute neutrophil count ≥1.5 × 10^9 cells/L; hemoglobin ≥90 g/L; platelets ≥100 × 10^9 cells/L • Liver function assessments: total bilirubin ≤1.5X ULN; AST and ALT ≤2.5X ULN (or ≤5X ULN for patients with liver metastases) • Renal function assessments: CK ≤1.5X ULN; creatinine ≤1.5X ULN or 24h creatinine clearance ≥0.84 mL/s·m^2 Exclusion criteria: • Previous HHI • Major surgery, antineoplastic therapy, or investigational agent ≤4 weeks before study initiation	Inclusion criteria: • Age ≥18 years • ECOG status ≤2 • For laBCC: ≥1 lesion with longest diameter ≥10 mm; prior radiation therapy unless contraindicated or inappropriate; lesion considered inoperable by specialist, or for which surgery is inappropriate due to recurrence after ≥2 surgeries, unlikely efficacy, or likely substantial morbidity or deformity • For mBCC: diagnosis confirmation based on tissue from metastasis, measurable disease with CT or MRI per RECIST Exclusion criteria: • Major organ dysfunction • Investigational agent ≤4 weeks before study initiation	Inclusion criteria: • Age ≥18 years • ECOG status ≤2 • For laBCC: histologically confirmed diagnosis, prior radiation therapy unless inappropriate, lesion considered inoperable • For mBCC: histologically confirmed diagnosis • Measurable or nonmeasurable disease per RECIST • Adequate organ function	Inclusion criteria: • Age ≥18 years • ECOG status ≤2 • At least 6 clinically measurable BCCs amenable to surgery, of which ≥3 had diameter ≥5 mm and ≥1 was histologically confirmed • Adequate organ function Exclusion criteria: • laBCC not amenable to surgery or radiation therapy, or mBCC
Treatment	• Randomization 1:2 to sonidegib 200 or 800 mg QD • Continued until disease progression, unacceptable toxicity, withdrawal of consent, study termination, or death • Interruptions ≥3 weeks allowed to manage toxicity • For 800 mg group, ≤2 dose reductions to 400 mg QD and 200 mg QD allowed • For 200 mg group, 1 dose reduction to placebo allowed	• Vismodegib 150 mg QD • Continued until disease progression, unacceptable toxicity, withdrawal of consent, study termination, or death • Interruptions ≥4 weeks allowed to manage toxicity	• Vismodegib 150 mg QD • Continued until disease progression, unacceptable toxicity, withdrawal of consent, study termination, or death • Interruptions ≥8 weeks allowed to manage toxicity	• Randomization 1:1 to: o Vismodegib 150 mg QD for 12 weeks, followed by 3 consecutive cycles of placebo QD for 8 weeks and vismodegib 150 mg QD for 12 weeks o Vismodegib 150 mg QD for 24 weeks, followed by 3 consecutive cycles of placebo QD for 8 weeks and vismodegib 150 mg QD for 8 weeks

TABLE 1. (CONTINUED)

Methodology of Major Studies Examining Efficacy and Safety of Sonidegib and Vismodegib				
	BOLT sonidegib	ERIVANCE vismodegib	STEVIE vismodegib	MIKIE vismodegib
Assessments	• Primary endpoint: ORR by central review • Secondary endpoints: ORR by investigator review, BOR by central and investigator review, DOR, PFS, TTR, and OS • Safety assessments: AE monitoring and grading per CTCAE v4.03, CK monitoring	• Primary endpoint: ORR by central review • Secondary endpoints: ORR by investigator review, BOR by central and investigator review, DOR, PFS, and OS • Safety assessments: AE monitoring and grading per CTCAE v3.0	• Primary endpoint: safety, including AE monitoring and grading per CTCAE v4.0, physical examination, ECOG status, vitals, and laboratory testing • Secondary endpoints: ORR per investigator review, DOR, TTR, PFS, OS	• Primary endpoint: Percent reduction from baseline in number of clinically evident BCCs at end of treatment (week 73) • Secondary endpoints: percent reduction in total size of target BCCs, recurrence or appearance of new BCCs, and ≥50% decrease in number of lesions • Safety assessments: AE monitoring
Tumor response criteria	• For mBCC, evaluation per RECIST v1.1 • For laBCC, evaluation per mRECIST criteria, integrating histology, MRI, and digital photography	• For mBCC, evaluation per RECIST v1.0 • For laBCC, CR was defined as absence of residual BCC in biopsy; PR, SD, and PD defined based on increase or decrease of externally visible or radiographic tumor dimension, or based on ulceration	• Assessed by physical examination per RECIST v1.1 every 4–8 weeks	• Assessed by physical examination and BCC counting every 8 weeks

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment; BOR, best overall response; CK, creatine kinase; CR, complete response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HHI, Hedgehog inhibitor; laBCC, locally advanced BCC; mBCC, metastatic BCC; mRECIST, modified RECIST; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; STEVIE, **S**afe**T**y **E**vents in **VI**smod**E**gib; TTR, time to tumor response; ULN, upper limit of normal.

Patients had histologically confirmed mBCC for which all other treatment options had been exhausted, or laBCC that was not amenable to radiation therapy, curative surgery, or other local therapies.[13] Adequate bone marrow, liver, and renal function as evidenced by standard laboratory assessments were also required for enrollment.[13] Exclusion criteria included previous treatment with an HHI.[13]

ERIVANCE enrolled patients aged ≥18 years with an ECOG Performance Status ≤2 with measurable mBCC according to Response Evaluation Criteria in Solid Tumors (RECIST), or laBCC with ≥1 tumor of ≥10 mm in the longest diameter.[14] For patients with mBCC, confirmation of the diagnosis with computed tomography (CT) or magnetic resonance imaging (MRI) was required.[14] For patients with laBCC, surgery was judged inappropriate if the tumor recurred after ≥2 curative surgeries or if curative resection was likely to result in substantial morbidity or deformity.[14]

Study Design

Study treatment included sonidegib 200 or 800 mg once daily (QD; 1:2 randomization, respectively) in BOLT, and vismodegib 150 mg QD in ERIVANCE.[13,14] Randomization in BOLT was stratified by geographic region, disease type (laBCC vs mBCC), and tumor histology for patients with laBCC (aggressive vs nonaggressive).[13] In both studies, treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, study termination, or death.[13,14] Dose interruptions of ≤3 weeks in BOLT and ≤4 weeks in ERIVANCE were permitted to manage toxic effects considered related to study treatment.[13,14] The BOLT study design also allowed dose reductions, limited to a maximum of 1 dose reduction to placebo for patients in the 200 mg group, and 2 dose reductions to 400 and 200 mg for patients in the 800 mg group.[13] The studies continued through 42 months for BOLT and 39 months for ERIVANCE.[11,12]

Assessments

In both studies, the primary efficacy endpoint was objective response rate (ORR) per central review.[13,14] Secondary efficacy endpoints included investigator-assessed ORR, central- and investigator-assessed best overall response (BOR, including complete response [CR], partial response [PR], and stable disease [SD]), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).[13,14] In BOLT, secondary efficacy assessments also included time to tumor response (TTR).[13] ERIVANCE only reported outcomes per investigator review in the final analysis.[12]

Evaluation of tumor response in mBCC used RECIST version 1.1 in BOLT and version 1.0 in ERIVANCE.[11,12] To evaluate laBCC lesion response in BOLT, modified RECIST (mRECIST) composite multimodal criteria were developed for use in the complex

setting of posttreatment scarring, fibrosis, and ill-defined lesion borders.[11] Evaluation per mRECIST integrated histology from multiple biopsies across lesion surface area, MRI according to RECIST v1.1, and standard and annotated color photography using bidimensional WHO criteria. According to mRECIST, criteria for CR included negative histology; MRI confirmation, if available; and CR, or PR or SD with tumor scarring or fibrosis only per lesion photograph.[15] Criteria for PR included negative histology; CR, PR, or SD per MRI, if available; and CR, PR, or SD with tumor scarring or fibrosis only per lesion photograph. Criteria for SD included positive or unknown histology; CR, PR, or SD per MRI, if available; and SD per lesion photograph if available.[15] Additionally, a prespecified analysis of BOLT results for patients with laBCC at 42 months was performed using a similar methodology to that used in the ERIVANCE trials in order to produce more comparative results for sonidegib vs vismodegib.

In ERIVANCE, CR was defined as absence of residual BCC in a biopsy specimen.[14] Criteria for PR included decrease of ≥30% in the externally visible or radiographic dimension of the tumor, or the complete resolution of ulceration if present at baseline. Progressive disease (PD) was defined as ≥20% increase in the externally visible or radiographic dimension, or the appearance of new ulceration or a new lesion. An increase or decrease in tumor size insufficient to adjudicate PR or PD was designated as SD. Externally visible tumor dimension measurements included scarring, and tumor response was confirmed 4 weeks after initial documentation.[14]

Safety assessments included adverse events (AEs) graded for toxicity using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for BOLT and 3.0 for ERIVANCE.[11,12] In BOLT creatine kinase (CK) levels were monitored ≤72 h from the first sonidegib dose, every week during the first 2 months, and every 4 weeks thereafter.[11]

Other Major Clinical Studies of Vismodegib Basal Cell Carcinoma

STEVIE (**S**afe**T**y **E**vents in **VI**smod**E**gib) was a phase 2, single-arm, open-label, multicenter study evaluating safety and efficacy of vismodegib in patients with advanced BCC in a setting representative of clinical practice (Table 1).[16] Eligible patients were ≥18 years old with an ECOG performance status ≤2 and histologically confirmed diagnosis of mBCC or laBCC not amenable to or appropriate for surgery and previously treated with radiotherapy, if appropriate.[16] Patients with both measurable and nonmeasurable disease per RECIST v1.1 were eligible to enroll if additional criteria were met. All patients received vismodegib 150 mg QD until disease progression, unacceptable toxicity, withdrawal of consent, study termination, or death. Treatment interruptions of ≤8 weeks were permitted to manage toxicity or if patients were unable to swallow capsules. The primary endpoint was safety, assessed by AE monitoring and grading for toxicity using CTCAE version 4.0, physical examination, ECOG performance status, vital signs, and laboratory testing. Secondary efficacy assessments included investigator-assessed ORR, DOR, TTR, PFS, and OS. Tumor response was assessed by physical examination using RECIST v1.1 every 4–8 weeks. CT and MRI were performed every 8–16 weeks, if necessary.[16]

MIKIE was a phase 2, randomized, double-blind, regimen-controlled, multicenter study evaluating the efficacy and safety of intermittent doses of vismodegib in patients with multiple BCCs (Table 1).[17] The study enrolled patients ≥18 years old with ECOG performance status ≤2 and >6 clinically evident BCCs amenable to surgery, and without any laBCC or mBCC tumors. Target BCCs (3 per patient) were ≥5 mm in their longest diameter, and at least 1 was histologically confirmed. Patients were randomized 1:1 into 2 treatment regimen groups. The 12-week regimen group received vismodegib 150 mg QD for 12 weeks, then 3 consecutive cycles of placebo QD for 8 weeks followed by vismodegib 150 mg QD for 12 weeks. The 24-week regimen group received vismodegib 150 mg QD for 24 weeks, then 3 consecutive cycles of placebo QD for 8 weeks followed by vismodegib 150 mg QD for 8 weeks. Both treatment groups were followed for 52 weeks after the end of the treatment period at week 73. The primary efficacy endpoint was percent decrease in number of BCCs at week 73.[17] Secondary efficacy endpoints included percent decrease in total size of target lesions, recurrence of appearance of new lesions, and ≥50% decrease in number of lesions.[17] Tumor response was assessed by physical examination and BCC counting every 8 weeks. AEs were classified using Medical Dictionary for Regulatory Activities v18.0.[17]

Despite key differences in study design and primary endpoints for the STEVIE and MIKIE trials as compared with BOLT and ERIVANCE, we believe the findings from these phase 2 trials provide value and are important trials to include when comparing efficacy and safety of sonidegib and vismodegib based on published literature to date.

Efficacy

Clinical efficacy

BOLT enrolled 79 patients in the sonidegib 200 mg group (66 with laBCC and 13 with mBCC) and 151 patients in the 800 mg group (128 with laBCC and 23 with mBCC).[11] The study population was 61% and 64% male with median age of 67 and 65 years, for the sonidegib 200 and 800 mg groups, respectively. At 42 months, 6 (8%) patients in the 200 mg group and 5 (3%) in the 800 mg group remained on treatment. Overall, 29 (37%) and 24 (16%) patients discontinued due to disease progression in the 200 and 800 mg groups, respectively.[11]

In the BOLT final analysis at 42 months, patients achieved ORR

by central review of 56% in laBCC and 8% in mBCC for the 200 mg group, and 46% in laBCC and 17% in mBCC for the 800 mg group (Table 2 and Figure 1). CR by central review reached 5% and 2% for patients with laBCC in the 200 mg and 800 mg groups, respectively, while CR for mBCC was 0% in both dose groups. Investigator-assessed ORR was 71% in laBCC and 23% in mBCC for the 200 mg group, with CR of 9% in laBCC and 0% in mBCC.[11] Using RECIST criteria, ORR by central review for patients with laBCC was 59.5% and 55.9% for the 200 and 800 mg groups, respectively, and CR was achieved by 19.0% and 33.3% of patients receiving 200 and 800 mg, respectively.

A total of 96 patients were included in the ERIVANCE efficacy analysis (63 with laBCC and 33 with mBCC), who were 61% male with median age of 62 years.[14] Eight patients with laBCC were excluded from the efficacy analysis because the diagnosis was not confirmed by an independent pathologist; these patients were included in the overall population. At 39 months, 8 (8%) patients remained on study treatment; the most common reason for discontinuation was disease progression, seen in 28 (28%) patients.[12] The ERIVANCE final analysis reported investigator-assessed ORR of 60% and 49%, including CR of 32% and 0%, for patients with laBCC and mBCC, respectively (Table 2 and Figure 1).[12]

A secondary analysis of ERIVANCE examined baseline disease severity and clinical benefit of vismodegib treatment in 61 patients with laBCC.[18] An independent review committee scored lesion photographs on a 5-point scale from 1 (no scarring and no functional impairment at baseline; significant worsening after treatment) to 5 (considerable deformity and functional impairment at baseline; significant clinical benefit after treatment). The majority of patients exhibited severe or moderate disease at baseline (59% scored 5, 13% scored 4), and significant or some clinical benefit after treatment (65% scored 5, 11% scored 4).[18]

FIGURE 1. Objective response rate from BOLT, ERIVANCE, and STEVIE.
BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment; CI, confidence interval; laBCC, locally advanced BCC; mBCC, metastatic BCC; ORR, objective response rate; QD, once daily; STEVIE, **S**afe**T**y **E**vents in **VI**smod**E**gib.

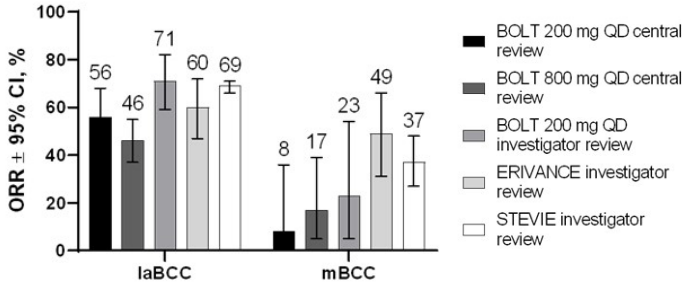

TABLE 2.

Efficacy Outcomes from BOLT and ERIVANCE Final Analyses, and STEVIE

	BOLT 42 months sonidegib						ERIVANCE 39 months vismodegib		STEVIE vismodegib	
	Central review				Investigator review		Investigator review		Investigator review	
	200 mg QD		800 mg QD		200 mg QD		150 mg QD		150 mg QD	
	laBCC n = 66	mBCC n = 13	laBCC n = 128	mBCC n = 23	laBCC n = 66	mBCC n = 13	laBCC n = 63	mBCC n = 33	laBCC n = 1077	mBCC n = 84
ORR, % (95% CI)	56 (43–68)	8 (0–36)	46 (37–55)	17 (5–39)	71 (59–82)	23 (5–54)	60 (47–72)	49 (31–66)	69 (66–71)	37 (27–48)
CR, % (95% CI)	5 (0.9–13)	0 (0–25)	2 (0–6)	0 (0–15)	9 (3–19)	0 (0–25)	32	0	33	5
DCR, %	91	92	82	91	91	85	84	91	94	83
DOR, median, months (95% CI)	26 (NE)	24 (NE)	23 (12–30)	NE (NE)	16 (12–20)	18 (18–18)	26 (9–38)	15 (6–17)	23 (20–27)	14 (9–NE)
PFS, median, months (95% CI)	22 (NE)	13 (6–33)	25 (19–33)	11 (7–17)	19 (17–24)	13 (9–19)	13 (10–28)	9 (7–17)	23 (21–26)	13 (12–18)
TTR, median, months (95% CI)	4 (4–6)	9 (NE)	4 (4–6)	1 (1–2)	4 (2–6)	NE	NR	NR	4 (3–4)	NE (6–NE)
OS, median, months (95% CI)	NR	NR	NR	NR	NR	NR	NE (NE)	33 (18–NE)	NR	NR

BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not evaluated; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; **S**TEVIE, Safe**T**y **E**vents in **VI**smod**E**gib; TTR, time to tumor response.

Overall, 1215 patients were included in the STEVIE efficacy and safety analyses, 1119 with laBCC and 96 with mBCC.[16] Patients were 57% male with median age of 72 years. At study completion, 147 (12%) patients remained on study treatment; 189 (16%) patients discontinued due to disease progression.[16] Investigator-assessed ORR was 69% in laBCC and 37% in mBCC, while CR reached 33% in laBCC and 5% in mBCC (Table 2 and Figure 1).[16]

Efficacy by age group

A secondary analysis in ERIVANCE patients examined efficacy of vismodegib stratified by age.[19] Patients aged ≥65 and <65 years demonstrated ORR by investigator review of 47% and 73% for laBCC, and 36% and 53% for mBCC, respectively. CR amounted to 26% for laBCC and 0% for mBCC in the ≥65 years group, and 36% for laBCC and 0% for mBCC in the <65 years group. The investigators concluded no clinically meaningful differences in efficacy were observed between the age groups.[19]

Efficacy outcomes from MIKIE

MIKIE enrolled 229 patients, 116 and 113 randomized to the 12-week and 24-week vismodegib regimen, respectively.[17] The 12-week regimen group was 70% male with a median age of 62 years, while the 24-week regimen group was 78% male with a median age of 60 years. Overall 64 (55%) and 56 (50%) patients remained on treatment by end of the study, and 3 (2.6%) and 3 (2.7%) patients discontinued due to disease progression, for the 12-week and 24-week regimen groups, respectively.[17]

Patients in MIKIE achieved mean 63% reduction in number and 83% reduction in size of BCCs on a 12-week vismodegib regimen, and 54% reduction in number and 69% reduction in size of BCCs on a 24-week vismodegib regimen.[17] Overall, 66% and 50% of the total number of patients in the 12-week and 24-week regimen groups had a ≥50% reduction in lesion number at the end of treatment, respectively. Absence of recurring or new BCCs at the end of treatment was reported in 77% and 74% of patients in the 12-week and 24-week regimens, respectively.[17]

Efficacy by tumor histology

Efficacy of sonidegib in aggressive and nonaggressive BCC subtypes was evaluated in a secondary analysis of BOLT results at 42 months.[20] Patients with aggressive BCC comprised 49% of the 200 mg and 50% of the 800 mg group, while those with nonaggressive BCC histology comprised 49% and 47% of the 200 and 800 mg groups, respectively.[20] Histology was indeterminate in 1% of patients in the 200 mg and 3% of patients in the 800 mg group. ORR by central review was 60% in patients with aggressive and 52% in patients with nonaggressive BCC receiving sonidegib 200 mg. For the 800 mg group, ORR was 45% in patients with aggressive and 47% in patients with nonaggressive BCC.[20] Among patients with aggressive BCC subtypes, those with infiltrative and morpheaform subtypes achieved the highest ORRs of 52% in the 200 mg and 37% in the 800 mg group for infiltrative, and 50% in the 200 mg and 75% in the 800 mg group for morpheaform BCC.[20]

Vismodegib efficacy in different histologic subtypes of high-risk or laBCC was examined in a phase 2b, single-center, prospective case series in 27 patients with a total of 65 BCCs.[21]

TABLE 3.

Adverse Events in >20% of Patients in BOLT 200 Mg Group, ERIVANCE, STEVIE, or MIKIE

	BOLT 42 months sonidegib		ERIVANCE 39 months vismodegib		STEVIE vismodegib		MIKIE vismodegib			
	200 mg QD n = 79		150 mg QD n = 104		150 mg QD N = 1215		12-week regimen n = 114		24-week regimen n = 113	
	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Any AE	43 (54)	34 (43)	45 (43)	58 (56)	660 (54)	531 (44)	113 (99)	Grade 3:30 (26) Grade 4:3 (3)	110 (97)	Grade 3:36 (32) Grade 4:4 (4)
Muscle spasms	(52)	(3)	68 (65)	6(6)	712 (59)	95 (8)	79 (69)	4 (4)	81 (72)	12 (11)
Alopecia	(50)	0	69 (66)	NA	731 (60)	16 (1)	72 (63)	0	73 (65)	0
Dysgeusia	(44)	0	58 (56)	NA	637 (52)	26 (21)	74 (65)	1 (0.9)	73 (65)	2 (2)
Nausea	(38)	(1)	34 (33)	0	214 (18)	4 (0.3)	23 (20)	0	14 (12)	1 (0.9)
Diarrhea	(30)	(1)	25 (24)	3(3)	189 (16)	8 (0.7)	20 (18)	0	17 (15)	1 (0.9)
CK increase	(24)	(6)	NR	NR	NR	NR	10 (9)	1 (0.9)	11 (10)	4 (4)
Weight decreased	(25)	(5)	45 (43)	9 (9)	444 (37)	48 (40)	23 (20)	1 (0.9)	21 (19)	0
Fatigue	(32)	(1)	40 (39)	5 (5)	181 (15)	20 (2)	24 (21)	0	26 (23)	0
Decreased appetite	(22)	(1)	26 (25)	3 (3)	283 (23)	20 (2)	21 (18)	0	15 (13)	2 (2)
Asthenia	NR	NR	NR	NR	267 (22)	24 (2)	15 (13)	0	19 (17)	1 (0.9)

Data presented as n (%).
AE, adverse event; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment; CK, creatine kinase; NA, not applicable; NR, not reported; QD, once daily; STEVIE, **S**afe**T**y **E**vents in **VI**smod**E**gib.

Examined lesions were 45% nodular, 37% infiltrative, and 15% superficial. Histological clearance after 12 weeks of treatment with vismodegib 150 mg QD was 45% in nodular, 75% in infiltrative, and 50% in superficial BCCs. Clinical clearance at 24 weeks was 83% for nodular, 92% in infiltrative, and 90% for superficial BCCs.[21] Another case series examined histologic changes in BCCs during vismodegib treatment and concluded vismodegib can promote a shift toward metatypical or squamous differentiation in patients with PR, and keratinization in patients with CR and PR.[22]

Relapse following complete response

Two retrospective studies examined relapse after discontinuation of vismodegib treatment in patients who achieved CR.[23,24] In the first study, 116 patients with laBCC, including those previously enrolled in STEVIE and MIKIE, reported a median (95% confidence interval [CI]) relapse-free survival of 18 (13–24) months after CR and end of vismodegib treatment.[23] After 36 months of follow-up, the relapse-free rate was 35%.[23] The second study in 35 patients with advanced BCC who received 6 months of vismodegib treatment reported a 31% relapse rate after a 6-month follow-up.[24]

There are no published studies evaluating relapse following discontinuation of sonidegib in patients who achieved CR.

Safety

Adverse events

At the time of BOLT completion, median duration of exposure to sonidegib was 11 months for the approved 200 mg dose.[11] Overall, 77 (98%) of BOLT patients receiving sonidegib 200 mg experienced an AE, with grade ≥3 AEs reported in 34 (43%) patients, and grade ≥3 AEs related to study treatment reported in 25 (32%) patients. Four (5%) patients experienced a serious AE (SAE) considered related to study treatment. AEs led to discontinuation in 24 (30%) patients.[11] Most common AEs (% of patients with grade ≤2 and grade ≥3 AEs) included muscle spasms (52% and 3%), alopecia (49% and 0%), and dysgeusia (44% and 0%, Table 3).

Median duration of exposure to vismodegib 150 mg QD was 13 months at the end of ERIVANCE, and all patients experienced an AE.[12] Of these, 58 (56%) patients experienced grade ≥3 AEs, and 9 (9%) experienced SAEs considered related to study treatment. Discontinuations due to AEs were reported for 22 (21%) patients, and the most common AEs were muscle spasms in 74 (71%) patients, alopecia in 69 (66%) patients, and dysgeusia in 58 (56%) patients (Table 3).[12]

In STEVIE, median duration of exposure to vismodegib 150 mg QD was 9 months and a total of 1192 (98%) patients experienced an AE.[16] Grade ≥3 AEs were reported in 531 (45%) patients, and SAEs in 289 (24%) patients. AEs led to discontinuation in 380 (31%) patients.[16] Muscles spasms in 807 (66%) patients, alopecia in 747 (62%) patients, and dysgeusia in 663 (55%) patients were the most common AEs (Table 3).

For all patients in MIKIE, exposure to vismodegib 150 mg QD was approximately 48 weeks.[17] A total of 113 (99%) and 110 (97%) patients experienced grade ≤2 AEs, 30 (26%) and 36 (32%) experienced grade 3 AEs, and 3 (3%) and 4 (4%) experienced grade 4 AEs, for the 12-week and 24-week regimen groups, respectively. SAEs related to study treatment occurred in 6 (5%) on the 12-week and 2 (2%) patients on the 24-week regimen. Discontinuations due to AEs were reported in 23 (20%) patients on the 12-week regimen and 30 (27%) patients on the 24-week regimen.[17] The most common AE was muscle spasms reported as grade ≤2 in 79 (69%) and 81 (72%) patients, and as grade 3 in 4 (4%) and 12 (11%) patients, for the 12-week and 24-week regimen groups, respectively (Table 3). Dysgeusia was second most common, reported as grade ≤2 in 74 (65%) and 73 (65%) patients, and 1 (1%) and 2 (2%) patients, for the 12-week and 24-week regimen groups, respectively. Alopecia was only grade ≤2, reported in 72 (63%) patients on a 12-week regimen and 73 (65%) patients on a 24-week regimen.

Based on published literature to date from the pivotal BOLT and ERIVANCE studies, sonidegib had a slightly lower incidence of most AEs, and AEs reported related to study treatment were slightly less frequent and less severe compared with vismodegib at final analysis.[12,15,25]

Safety by age group

In a secondary analysis of vismodegib safety in ERIVANCE patients stratified by age, median exposure to study drug was 9 months in patients ≥65 years and 10 months in patients <65 years.[19] All patients in both age groups experienced ≥1 AE, and grade ≥3 AEs were reported in 24 (51%) patients aged ≥65 and 20 (35%) patients aged <65 years. AEs led to discontinuation in 7 (15%) and 6 (11%) patients, for the ≥65 and <65 groups, respectively. Most common AEs (n [%] of patients aged ≥65 vs <65 years) included muscle spasms (30 [64%] vs 41 [72%]), dysgeusia (24 [51%] vs 29 [51%]), and alopecia (23 [49%] vs 43 [75%]).[19]

Muscle spasms and creatine kinase elevation

Creatine kinase is an enzyme found in abundance in muscle tissue, where it reversibly phosphorylates creatine using adenosine triphosphate as a phosphate source.[26] In the event of cellular stress or damage, such as during spasmic contractions, muscle cells can release their content into the bloodstream, resulting in serum CK elevation.[27]

The exact relationship between muscle spasms and Hedgehog inhibition is not known, but it is hypothesized that noncanonical Hedgehog signaling may lead to calcium influx into the muscle

cell.[28,29] Interestingly, significant reduction of muscle cramps was observed in 8 patients treated with vismodegib who were co-administered the calcium channel blocker amlodipine.[30]

Muscle spasms were the most common AE in the BOLT, ERIVANCE, STEVIE, and MIKIE studies.[11,12,16,17] They were reported in 43 (54%) patients receiving sonidegib 200 mg in BOLT, 74 (71%) patients in ERIVANCE, 807 (66%) patients in STEVIE, and 79 (69%) and 81 (72%) patients (grade ≤2 only) in the MIKIE 12-week and 24-week regimen groups, respectively.[11,12,16,17] The majority of muscle spasms were grade 1 or 2, with 2.5% of patients experiencing grade ≥3 muscle spasms in the BOLT 200 mg group, 6 (5.8%) patients in ERIVANCE, 95 (8%) in STEVIE, and 4 (4%) and 12 (11%) patients in the MIKIE 12-week and 24-week regimen groups, respectively.[11,12,16,17] Guidelines for managing muscle-related AEs with dose reductions and interruptions were developed during the BOLT study, for treating patients receiving sonidegib.[31]

Safety assessments in BOLT included routine monitoring of CK levels. Grade <3 CK elevation was reported as an AE in 24%, of patients, while grade ≥3 CK elevation was reported in 6% of patients receiving sonidegib 200 mg.[11] CK monitoring was not part of the ERIVANCE protocol, and the number of patients with serum CK elevation was not reported in the final analysis.[12] In STEVIE, ≥1 evaluable CK measurement was available for a subset of 180 (15%) patients.[16] Among 121 patients with ≥1 CK measurement who did not experience muscle spasms, an AE of elevated CK levels was reported in 44 (36%) patients, and grade ≥3 CK elevation was reported in 4 (3%) patients.[16] Among 59 patients with ≥1 CK measurement who experienced muscle spasms, 20 (34%) experienced elevated CK levels and 2 (3%) had grade ≥3 CK elevation. In MIKIE, grade ≤2 CK elevation was reported in 10 (9%) and 11 (10%) patients, and grade 3 in 1 (1%) and 4 (4%) patients, for the 12-week and 24-week regimen groups, respectively.[17]

Alopecia

During hair follicle morphogenesis, the Hedgehog pathway promotes the expansion of the follicular epithelium in response to an upstream signal from the canonical Wingless (Wnt) pathway.[32] Abnormal Hedgehog activation in BCC is associated with abnormal Wnt pathway activation and upregulation of Wnt target genes, constituting a reversal of the Wnt-Hedgehog relationship in the healthy developing organism.[32]

Alopecia is commonly observed with sonidegib and vismodegib treatment, and is thought to occur due to blocked transition to the anagen phase in the hair follicle after telogen phase hair shedding.[32] Compared with hair loss due to chemotherapy, alopecia due to HHI treatment has a longer time to onset, and manifests as gradual hair thinning.[32] Alopecia was observed in 39 (49%) patients in BOLT who received sonidegib 200 mg, 69 (66%) patients in ERIVANCE, 747 (62%) patients in STEVIE, and 72 (63%) and 73 (65%) patients in the MIKIE 12-week and 24-week regimen groups.[11,12,16,17]

Dysgeusia and weight loss

Dysgeusia was reported in 44% patients in the BOLT 200 mg group, 58 (56%) in ERIVANCE, 663 (55%) in STEVIE, and 75 (66%) in each of the MIKIE treatment groups.[11,12,16,17] Grade <3 and grade ≥3 weight loss was experienced by 25% and 5% of patients in the BOLT 200 mg arm, respectively.[11] Weight loss was reported in 54 (52%) patients in ERIVANCE, 493 (41%) in STEVIE, and 24 (21%) and 21 (19%) in the MIKIE 12-week and 24-week regimen groups.[12,16,17] Nutritional management has been suggested to mitigate weight loss and malnutrition in patients treated with HHIs.[33]

Pharmacokinetics

The PK of sonidegib was studied in healthy volunteers, patients with advanced solid tumors, and patients from the BOLT study. Sonidegib reaches peak concentration in plasma within 2–4 hours of dosing, and has a large apparent volume of distribution of approximately 9000–33000 L and an elimination half-life of 30–41 days.[34-36] In patients from the BOLT study, steady state of sonidegib in plasma was achieved by week 17 of treatment for both the 200 and 800 mg QD doses.[15] Absorbed sonidegib is metabolized predominantly by CYP3A4, while unabsorbed sonidegib is eliminated in excreta.[36,37] Co-administration with the proton pump inhibitor esomeprazole results in a modest reduction of sonidegib absorption and no metabolic drug-drug interaction, suggesting stomach acidity has no substantial impact on sonidegib bioavailability.[38] PK exposure-safety analyses suggests lower exposure to sonidegib correlates with lower risk of grade ≥3 CK elevation.[39]

Vismodegib PK was investigated in healthy volunteers, and in patients with refractory, locally advanced, or metastatic solid tumors. Vismodegib has an elimination half-life of 4–12 days, reaches peak plasma concentration approximately 2 days after a single dose and steady state within 7–21 days of repeated dosing, and has a volume of distribution of approximately 16–27 L.[8,40,41] More than 99% of vismodegib in plasma binds serum albumin and alpha-1-acid glycoprotein, therefore administration of doses greater than 150 mg QD does not result in an increase of unbound steady-state plasma concentration.[40,42] Vismodegib administration 3 times per week or weekly is not sufficient to achieve an efficacious plasma concentration.[43]

Sonidegib appears to be highly lipophilic due to its large volume of distribution. Resultantly, steady-state levels of sonidegib are 6 times higher in skin than in plasma.[5] In contrast, the smaller volume of distribution of vismodegib indicates that it is predominantly confined to plasma. The differing volumes of distribution for sonidegib and vismodegib may potentially

explain observed differences in efficacy and toxicity between these two HHIs.

Efficacy and Safety in Patients With Nevoid Basal Cell Carcinoma Syndrome

Patients with the hereditary disease nevoid basal cell carcinoma syndrome (NBCCS) tend to develop multiple BCCs from a young age.[44] Since multiple surgeries can be costly and result in deformity and emotional distress, HHIs are investigated as a potential treatment option for this patient population.

A phase 2, double-blind, randomized, placebo-controlled exploratory study evaluated preliminary efficacy and safety of sonidegib in patients with NBCCS.[45] Twelve weeks of treatment resulted in histological clearance of target BCCs in 4 of 7 patients, and clinical clearance in 3 of 7 patients treated with sonidegib 400 mg QD, vs 0 of 2 patients treated with placebo. The total number of BCCs in the sonidegib group decreased from 566 at baseline to 341 after 12 weeks of treatment and to 309 after 4 additional weeks of follow-up. AEs were reported in 7 of 8 patients treated with sonidegib, the most common AE being muscle spasms in 3 patients. Alopecia and CK elevation were reported in 2 patients each.[45]

Vismodegib efficacy and safety in patients with NBCCS was evaluated in a phase 2 double-blind, randomized, placebo-controlled study.[46] Treatment over 36 months resulted in a mean rate of appearance of new surgically eligible BCCs per-patient-per-year of 2 in 26 patients treated with 150 mg QD vismodegib vs 34 in 15 patients treated with placebo. Most common AEs in patients treated with vismodegib were muscle spasms and alopecia in 100% of patients, and dysgeusia in 93% of patients.[46]

Resistance to Treatment

A subset of patients treated with sonidegib or vismodegib exhibit lack of response (primary resistance), or develop resistance after initial response to treatment (secondary resistance).[47] In the BOLT 42-month analysis, the rate of PD in patients with laBCC was 9% in the 200 mg and 18% in the 800 mg sonidegib group.[11] Patients in ERIVANCE exhibited a rate of PD of 6% in laBCC and 2% in mBCC at 39 months.[12]

An open-label, single-arm, proof-of-concept study examined the efficacy of sonidegib and buparlisib in 7 patients with advanced BCC that did not respond to previous treatments, including treatment with vismodegib.[48] Treatment resulted in PR in 1, SD in 4, and PD in 2 patients. The study was terminated early due to toxicity.[48]

The efficacy of sonidegib in 9 patients with advanced BCC resistant to vismodegib was evaluated in an open-label, investigator-initiated study.[49] Treatment for a median duration of 6 weeks resulted in SD in 3 and PD in 5 patients. Most common AEs included muscle spasms in 5, nausea in 4, and CK elevation in 2 patients.[49]

CONCLUSIONS

Although clinical studies of sonidegib and vismodegib have distinct methodologies, they demonstrate similarities in efficacy and the AEs commonly encountered, including muscle spasms, elevated CK, alopecia, and dysgeusia. Sonidegib and vismodegib demonstrate differences in their PK profiles, with a trend towards longer half-life for sonidegib and a tendency for vismodegib to bind plasma proteins. Management of BCCs in patients with NBCCS and patients who develop resistance to HHIs are topics of ongoing interest.

DISCLOSURES

M. Migden has participated on advisory boards and received honoraria from Genentech; Novartis Pharmaceuticals Corporation; Regeneron Pharmaceuticals; and Sun Pharmaceutical Industries, Inc. A. Farberg has participated on advisory boards and received honoraria from Ortho-dermatologics; Sensus; and Sun Pharmaceutical Industries, Inc. R. Dummer has participated on advisory boards and consulted for Amgen; Bristol-Myers Squibb; Catalym; Merck Sharpe and Dohme; Novartis Pharmaceuticals Corporation; Pierre Fabre; Roche; Sanofi; Second Genome; Sun Pharmaceutical Industries, Inc.; and Takeda. N. Squittieri is an employee of Sun Pharmaceutical Industries, Inc. C. W. Hanke participated in advisory boards for Sun Pharmaceuticals, Inc.; and has received research grants for clinical trials from Sun Pharmaceuticals, Inc.

Author's contributions: All authors met the International Council of Medical Journal Editors criteria and received neither honoraria nor payment for authorship.

Funding: Research was funded by Sun Pharmaceutical Industries, Inc. (Princeton, NJ).

ACKNOWLEDGMENT

Writing and editorial support for manuscript preparation were provided by Zehra Gundogan, VMD (AlphaBioCom, LLC, King of Prussia, PA).

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AUTHOR CORRESPONDENCE

Michael Migden MD

E-mail:..... mrmigden@mdanderson.org