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Quality of Life for Patients with Advanced Basal Cell Carcinoma Treated with Hedgehog Signaling Pathway Inhibitors

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Abstract

Basal cell carcinoma (BCC), the most common form of cancer, affects approximately 2 million people annually in the US. Aberrant activation of the hedgehog signaling pathway plays an important role in BCC. Two inhibitors of the SMO component of hedgehog signaling, vismodegib and sonidegib, are currently approved for use in advanced BCC, including locally advanced BCC (laBCC) and metastatic BCC (mBCC), depending on the country of approval. Location of lesions and fears about changes in appearance may affect the quality of life (QoL) of patients with advanced BCC. In addition, QoL itself is an outcome for advanced BCC. The key clinical trials for vismodegib (ERIVANCE and STEVIE) and for sonidegib (BOLT) included QoL as secondary end points, using different questionnaires for assessment. In ERIVANCE, Short Form-36 for assessing QoL showed no changes from baseline on either the physical or emotional domains. In STEVIE, the Skindex-16 for assessing QoL showed that treatment with vismodegib was associated with clinically meaningful improvement in the emotional domain. To determine QoL, BOLT used predetermined subscales related to skin specifically from the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC H&N35. Both the QLQ-C30 and H&N35 selected subscales showed either maintenance or improvement from baseline. Factors affecting QoL during treatment of patients with advanced BCC include baseline QoL, having fewer comorbidites, and having better initial mental health status. In addition, patients whose lesions were advanced, but were not as large as others or not located in visible areas (ie, head and neck) reported better QoL. Treatment-emergent adverse events (AEs) have an impact on QoL in patients with advanced BCC. Most of the AEs reported in trials for vismodegib and sonidegib were grade 1-2. Using techniques to manage AEs effectively may help improve QoL for those whose QoL decreases during treatment.

Keywords: Basal cell carcinoma; Sonidegib; Quality of life; Vismodegib

Introduction

Basal cell carcinoma (BCC) is the most common form of cancer, affecting approximately 2 million people annually in the United States. The worldwide incidence of BCC is increasing [1]. Caucasian males older than 65 years are at highest risk for developing BCC [2], and the overall risk increases with exposure to ultraviolet radiation from sun exposure [1]. Most cases of BCC can be cured with Mohs surgery, wide local excision, electrodessication and curettage, or other destructive modalities. In addition, radiation as a single modality may be appropriate for patients who have multiple comorbidities and/or are adamantly averse to surgery. Such patients may include those who are elderly or in poor general health [3]. Advanced types of BCC, defined as locally advanced BCC (laBCC) and metastatic BCC (mBCC), require other treatment modalities. The median survival times for advanced BCC remain relatively short, ranging from approximately 8 months to 54 months [4,5].

The aberrant activation of the hedgehog signaling pathway plays an important role in the pathophysiology of BCC. Mutations in the components PTCH, SMO, and others lead to constant activation of hedgehog signaling, with resulting effects on cell survival, proliferation, and invasion (Figure 1) [6,7]. Somatic mutations in *PTCH* and *SMO* that trigger constitutive hedgehog pathway activation were found in BCC [8,9]. Based on these observations, hedgehog pathway signaling inhibitors were developed for use in BCC.

The SMO component of the hedgehog signaling pathway has been amenable to targeting by antagonists, with 2 SMO inhibitors, vismodegib and sonidegib, currently approved for use in advanced BCC, either for laBCC alone or for laBCC and mBCC; depending on the country and the regulatory agency decision (Table 1). In the ERIVANCE trial at 30 months, patients with laBCC or mBCC showed investigator-assessed objective response rates of 60.3% and 48.5%, respectively [10]. In the BOLT study, patients treated with sonidegib at 30 months showed objective response rates of 71.2% for laBCC and 23.1% for mBCC (per investigator review) [11].

Country	Agency	Date	Indication
Australia	Therapeutic Goods Administration	August 2015	advanced BCC[a]
European Union	European Medicines Agency	August 2015	locally advanced BCC
Switzerland	Swissmedic	June 2015	advanced BCC
United States	Food & Drug Administration	July 2015	locally advanced BCC

Table 1: Sonidegib Approvals. [a]Advanced BCC includes locally advanced and metastatic BCC. BCC indicates basal cell carcinoma.

Because advanced BCC is associated with sun exposure, it occurs often on visible parts of the body, such as the face, ears, and neck [12]. Treatment involving the physical removal of lesions, such as electrodessication and curettage, excision, and Mohs micrographic surgery, may, depending on the size and location of the lesions, affect patient appearance [13]. Location of lesions and fears about changes in appearance may affect the quality of life (QoL) of patients with BCC [14]. In addition, QoL may itself be an outcome for the management of BCC [15]. Also, practitioners find that the degree of visible skin disease and posttreatment appearance does not always correlate with its impact on patients' QoL: some patients may be very distressed by what appears as mild clinical involvement [16].

To assess more accurately QoL issues associated with advanced BCC, specific QoL questionnaires for patient-reported outcomes during management of BCC were developed. Results show that patients had concerns regarding future procedures to treat their disease (29%), and that many experienced sadness (21%) or depression (36%) [17]. Based on these observations, the impact of hedgehog inhibitors in advanced BCC on patients' QoL warrants discussion. The goal of this review is to discuss the current literature on QoL regarding the 2 approved hedgehog inhibitors in patients with advanced BCC, emphasizing recent data from clinical trials.

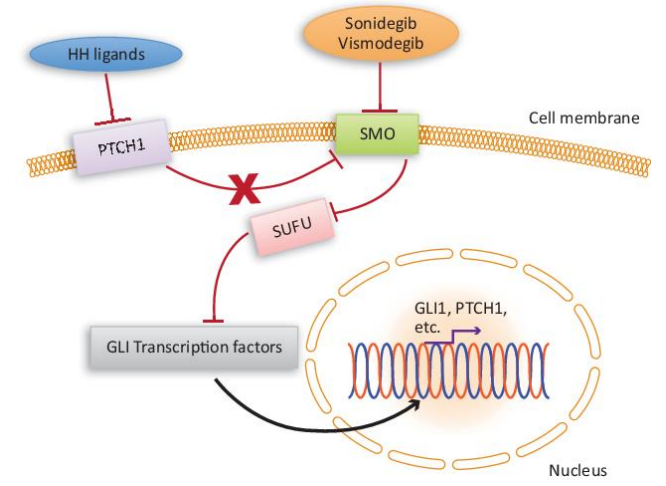

Figure 1: Hedgehog Pathway Signaling in Cancer: Vismodegib and Sonidegib Inhibit SMO Component. Hedgehog signaling leads to downstream activation of genes involved in cancer cell metastasis, proliferation, and survival. Vismodegib and sonidegib inhibit the smoothened component of the hedgehog signaling pathway. Reproduced and adapted from [34], with permission. BMP indicates bone morphogenetic protein; GLI, glioma-associated oncogene; HH, hedgehog; IGF, insulin-like growth factor; PTCH, patched; SMO, smoothened; SUFU, suppressor of fused.

Vismodegib: QoL data from the ERIVANCE and STEVIE trials

In the United States, approval of vismodegib for advanced BCC was based on data from the ERIVANCE clinical trial (NCT00833417; Table 2), a pivotal phase 2 study. ERIVANCE was a single-arm, 2-cohort study that enrolled 104 patients with advanced BCC: 71 with laBCC and 33 with mBCC (Table 2) [18,19]. As assessed by an independent review committee, the objective response rate was 43% for patients with laBCC (21% had complete responses) and 30% for patients with mBCC (no complete responses) [19]. In ERIVANCE, treatment-associated AEs included muscle spasms (68%, any grade), alopecia (63%, any grade), and dysgeusia (51%, any grade) [19]. In addition, cutaneous AEs have occurred with vismodegib use, such as alopecia (66%, any grade), squamous cell carcinoma (12%, any grade), and pruritus (11%, any grade) [20].

As one of its secondary end points, ERIVANCE measured changes in QoL, as assessed by changes from baseline on the Short Form (SF)-36 questionnaire. This single-page questionnaire asks 36 questions across 8 domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy or fatigue, emotional well-being, social functioning, pain, and general health. A higher positive score on the SF-36 indicates better QoL [21]. The SF-36 was not designed to assess the QoL associated with skin disease but is a general assessment of QoL. By the end of study, patients showed no positive changes from baseline on either the physical or emotional portions of the SF-36 (Table 3).

STEVIE (Study of Vismodegib in Patients with Locally Advanced or Metastatic Basal Cell Carcinoma; NCT01367665) was a multicenter, open-label, postapproval clinical trial comprising the largest patient series with advanced BCC at the time. Data from 499 participants with laBCC and 31 participants with mBCC were analyzed after 12 months on study. The primary end point was the percentage of participants who experienced any AEs, grade 3 or 4 AEs, AEs leading to drug interruptions or discontinuations, or any serious AEs [22]. As assessed by investigators, 302 participants with laBCC had a response: 153 patients had a complete response, and 149 patients had a partial response; 11 patients with mBCC had a response: two had a complete response and nine had a partial response [22].

Treatment-emergent AEs occurred in 307 patients (98%; n=314) who had <12 months of exposure and in 184 patients (99%; n=185) who had ≥12 months of exposure [22]. The most common treatment-emergent AEs in patients with ≥12 months exposure included muscle spasms (80%), alopecia (83%), dysgeusia (70%), weight loss (44%), and asthenia (35%) [22].

A secondary end point in the STEVIE trial was QoL assessment, using the Skindex-16 questionnaire [16]. This single-page questionnaire comprises a set of skin-related QoL questions that ask patients how often they are bothered by various aspects of their disease. In addition, the Skindex-16 aggregates scores in key areas, symptoms, emotions, and functioning [16]. In the STEVIE study, results from the Skindex-16 questionnaire showed that patients given vismodegib had clinically meaningful improvement in the emotional domain.

Sonidegib: QoL data from the BOLT trial

Approval of sonidegib was based on data from a pivotal phase 2 trial, BOLT (Basal cell carcinoma Outcomes with LDE225 [sonidegib] Treatment, NCT01327053; Table 2) clinical trial. In BOLT, patients with laBCC not amenable to curative surgery or radiation or patients with mBCC, for which all available treatment options had been exhausted, were randomized to receive 200 mg or 800 mg sonidegib once daily (QD) in a 1:2 ratio. Assessments of response in BOLT were performed by both a central review committee and by the investigators for the duration of the trial.

Trial name, NCT #	Drug	Phase, N, arms	Primary end point(s)	QoL data gathered
STEVIE NCT01367665	vismodegib	Phase 2, single arm, N=501[b]	Percentage of participants who experienced any AEs, grade 3 or 4 AEs, AEs leading to drug interruptions or discontinuations, or any serious AEs	Skindex-16 questionnaire (secondary end point)
ERIVANCE NCT00833417	vismodegib	Phase 2, single-arm, N=104	OR by independent review	SF-36, version 2 (secondary end point)
BOLT NCT01327053	sonidegib	Phase 2, two arms: sonidegib 200 or 800 mg QD, N=229	ORR by 6 months, based on mRECIST for laBCC; OR by 6 months based on mRECIST for mBCC	EORTC QLQ-C30 and EORTC H&N35 (secondary end points)

Table 2: Clinical Trials[a] for Approved Hedgehog Inhibitors. [a]Clinical trial data available at https://clinicaltrials.gov; retrieved July 25, 2017. [b]501 patients enrolled but 2 patients did not receive study drug. AE indicates adverse event; EORTC, European Organisation for Research and Treatment of Cancer; H&N35, Head and Neck Cancer Module 35; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OR, objective response; ORR, objective response rate; QD, daily; QLQ-C30, Quality of Life Questionnaire-Core 30; QoL, quality of life; SF-36, Short Form-36 Health Survey.

After enrollment and randomization, 230 patients were treated. From the analysis at 30 months in patients with laBCC, the objective response rates (ORRs) in the 200-mg arm were 56.1% (central review) and 71.2% (investigator review); in the 800-mg arm, ORRs were 45.3% and 58.6%, respectively. From the analysis at 30 months in patients with mBCC, ORRs in the 200-mg arm were 7.7% (central review) and 23.1% (investigator review); in the 800 mg arm, the ORRs were 17.4% (central review) and 34.8% (investigator review), respectively [11].

	Wk 12	Wk 24	EOS
n	82	75	20
Change in MCS score	2.20	2.29	–3.80
Range	–0.22 to 4.62	0.05-4.53	–10.55 to 2.96
Change in PCS score	–1.25	–1.90	–2.86
Range	–2.86 to 0.36	–3.75 to 0.05	–7.39 to 1.66

Table 3: Change from Baseline on the SF-36[a] QoL Questionnaire. [a]The SF-36 Health Survey (version 2) uses patient-reported symptoms on 8 subscales to assess QoL. The Physical Component Summary (PCS) score summarizes the subscales physical functioning, role−physical, bodily pain, and general health. The Mental Component Summary (MCS) score summarizes the subscales vitality, social functioning, role −emotional, and mental health. Each score was scaled from 0 to 100. A positive change score indicates better QoL. EOS indicates end of study. Source: Data from the ERIVANCE trial data, NCT00833417, available at https://clinicaltrials.gov; retrieved July 28, 2017.

Fewer AEs leading to dose interruptions or reductions (25 [32%] of 79 *vs.* 90 [60%] of 150), or treatment discontinuations (17 [22%] *vs.* 54 [36%]) occurred among patients in the 200-mg QD arm than in the 800-mg QD arm [23]. The most frequent AEs leading to treatment discontinuation were muscle spasm (3 [4%] in the 200-mg group *vs.* 13 [9%] in the 800-mg group), dysgeusia (2 [3%] *vs.* 7 [5%]), weight decrease (2 [3%] *vs.* 7 [5%]), and nausea (2 [3%] *vs.* 6 [4%]). Serious AEs were reported in 11 (14%) of the 200-mg group and 45 (30%) of the 800-mg QD group. The most frequently reported cutaneous AE was alopecia (49% in the 200-mg group and 58% in the 800-mg group) [23]. The most frequently reported serious AEs were rhabdomyolysis (1 [1%] of 79 in the 200 mg group and 3 [2%] of 150 in the 800-mg group) and elevated creatine kinase levels (1 [1%] in the 200-mg group and 5 [3%] in the 800-mg group) [23]. It should be noted that no cases of rhabdomyolysis (defined as creatine kinase elevations >10-fold higher than the pretreatment or baseline level [or >10 times the upper limit of the normal range if no baseline level was reported] in conjunction with a 1.5-fold increase from baseline in serum creatinine) were confirmed by an independent safety review committee composed of experts on muscle toxicity [23]. With 30 months of data, sonidegib showed a similar AE profile to that seen at 18 months [11,23].

In BOLT, QoL was assessed using relevant predetermined subscales of the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) data [24] and the EORTC H&N35 (EORTC Quality of Life Module for Head and Neck Cancer) data [25]. Used together, the predetermined subscales of these questionnaires were intended to be informative assessments of QoL during the BOLT trial.

At 12 months, the majority of patients had maintenance of or improvement in predetermined subscale scores on the EORTC QLQ-C30 and the EORTC H&N35. These improvements in QLQ-C30 and H&N35 were found to be consistent across both laBCC and mBCC cohorts (Figure 2 and Table 4). This analysis showed maintenance or improvement in each predetermined subscale through week 73 for patients taking 200 mg or 800 mg sonidegib [23,26,27]. The results of the EORTC H&N35 showed the most improvement in the domain of trouble with social contact (Figure 2), an indication that sonidegib treatment may have improved some patients' concerns regarding the effect of advanced BCC on their appearance.

Discussion

The visible extent of nonmelanoma skin cancer, such as BCC, on QoL often does not correlate with the degree that patients feel disturbed by their disease [16]. In one study, patients with basal cell nevus syndrome attending a national conference were asked to complete 2 questionnaires, the Skindex-29 and the Center for Epidemiological Studies Depression Scale. Of the patients who responded, the median score on the Skindex-29 was higher than for a

cohort of patients with neurofibromatosis, and 50% of patients with basal cell nevus syndrome had significant symptoms of depression [28].

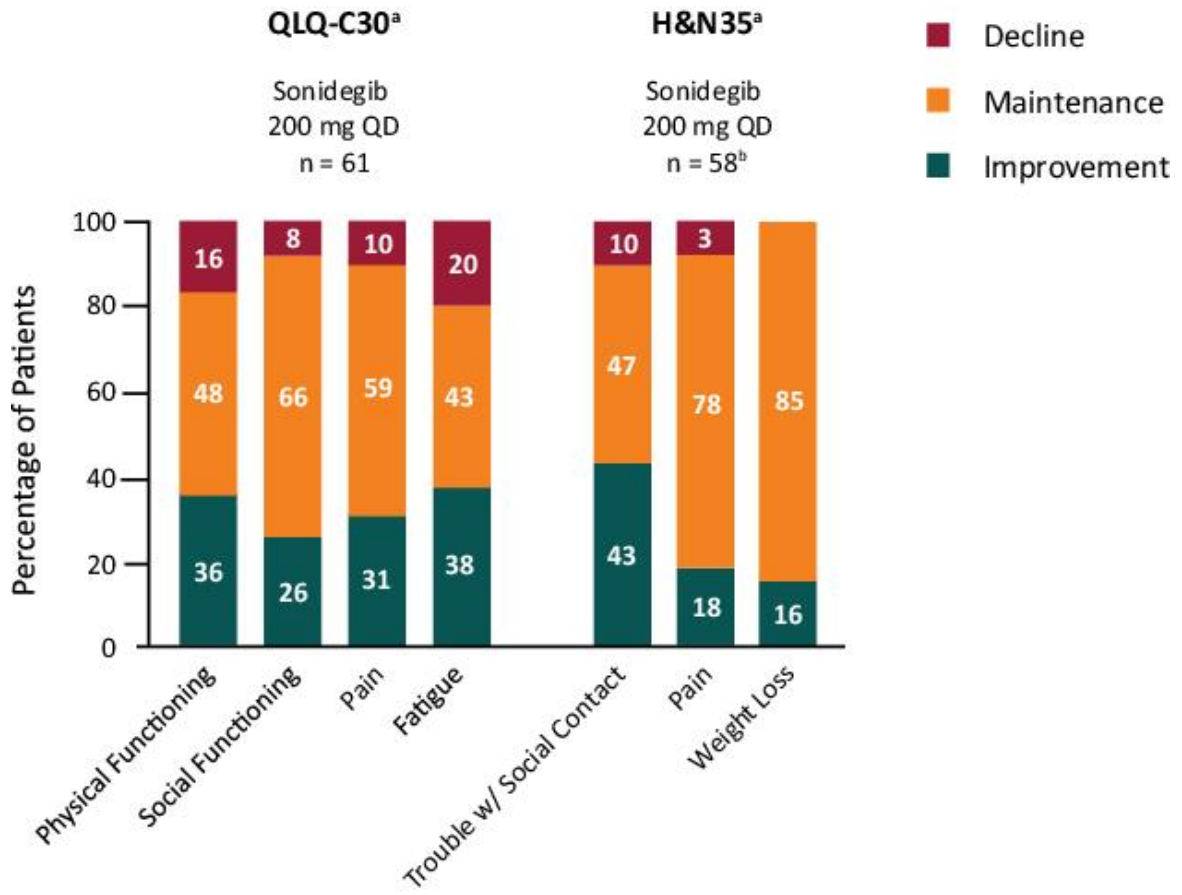

Figure 2: Locally Advanced Basal Cell Carcinoma Quality of Life from BOLT Trial. EORTC QoL results for patients with laBCC from BOLT. At 12 months, most patients with laBCC had maintenance of or improvement in scores on the EORTC QLQ-C30 and EORTC H&N35. A smaller proportion of responders reported a decline from baseline than nonresponders. Data from [23,26,27]. [a]Based on best reported post baseline score; [b]n=60 for head and neck pain. EORTC H&N35 indicates European Organisation for Research and Treatment of Cancer Quality of Life Module for Head and Neck Cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; laBCC, locally advanced basal cell carcinoma; QD, once daily.

Various studies have reported opposing results using different QoL questionnaires. In one study of 84 patients with BCC from Brazil who had used sunscreen for >5 years, those who had ulcerated tumors, had tumors >2 cm, or had tumors located on the body other than the head (eg, neck, trunk, upper limbs, or lower limbs) scored poorest on the Dermatology Life Quality Index [29]. However, another study of 633 patients from the United States showed factors affecting QoL were baseline QoL, fewer comorbidities, and better initial mental health status. In addition, patients whose lesions were not very large or not located in visible areas (ie, head and neck) reported better QoL on the Skindex-16 [14].

In a study conducted across 5 centers, patients with advanced BCC were administered a newly developed questionnaire specific for advanced BCC to determine patient concerns and sources of distress. Among the most distressing aspects reported were appearance, weight loss, feeling loss of control, having a sense of doom, and being distraught that treatment was not sought earlier [17]. The patients reported feeling sad, depressed, or using antidepressants more often than for other aspects of the emotional domain of the questionnaire [17].

Among patients at a Department of Veterans Affairs Medical Center, the risk for BCC and history of previous BCC, as well as concerns about sun damage contributing to future disease contributed to worse skin-related QoL. The investigators suggest that counseling patients may help improve their QoL [30].

Finally, the impact that AEs arising from therapy for advanced BCC have on QoL should be discussed. Unlike some targeted therapies used for other types of cancer (eg, sorafenib, imatinib), which can cause multiple cutaneous AEs (eg, hypopigmentation, maculopapular rash, epidermoid cysts) [31,32], hedgehog signaling pathway inhibitors primarily produce alopecia as a cutaneous AE [32]. Common noncutaneous AEs from hedgehog inhibitors include muscle spasm, dysgeusia, fatigue, and nausea [20,23]. Moreover, although the

majority of the AEs reported in trials for vismodegib and sonidegib were grade 1-2, it should be noted that patients may take either of these drugs long term, so limiting AEs and maintaining high QoL should be part of treatment goals.

n (%)	Sonidegib 200 mg QD	Sonidegib 800 mg QD
EORTC QLQ-C30		
Physical functioning	n=13	n=20
Improvement from baseline, n (%)	9 (69)	8 (40)
No improvement from baseline, n (%)	3 (23)	10 (50)
Social functioning	n=13	n=20
Improvement from baseline, n (%)	5 (39)	7 (35)
No improvement from baseline, n (%)	6 (46)	12 (60)
Pain	n=13	n=20
Improvement from baseline, n (%)	6 (46)	11 (55)
No improvement from baseline, n (%)	7 (54)	7 (35)
Fatigue	n=13	n=20
Improvement from baseline, n (%)	6 (46)	8 (40)
No improvement from baseline, n (%)	6 (46)	8 (40)
EORTC H&N35		
Trouble with social contact	n=13	n=19
Improvement from baseline, n (%)	4 (31)	8 (42)
No improvement from baseline, n (%)	7 (54)	9 (47)
Head and neck pain	n=13	n=20
Improvement from baseline, n (%)	3 (23)	4 (20)
No improvement from baseline, n (%)	9 (69)	12 (60)
Weight loss	n=12	n=19
Improvement from baseline, n (%)	2 (17)	5 (26)
No improvement from baseline, n (%)	8 (67)	14 (74)

Table 4: Predetermined Subscales of EORTC QLQ-C-30 and H&N35 Results for Patients with Metastatic Basal Cell Carcinoma from BOLT Trial. The BOLT trial has pre-specified QoL end points as part of the trial design. To measure QoL, patients responded to predetermined subscales of the EORTC QLQ-C30 and the EORTC H&N35. Data from [26]. EORC H&N35 indicates European Organisation for Research and Treatment of Cancer Quality of Life Module for Head and Neck Cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

Using effective techniques to manage AEs may help improve QoL for those patients who experience decreased QoL because of their treatment. For example, treating weight loss and dysgeusia may involve consultation with a dietitian, alopecia may be treated with 5% minoxidil twice daily or finasteride (1 mg daily for men; 5 mg daily for women), and diarrhea may be treated with loperamide 2 mg up to 16 mg daily [33]. The treatment of muscle spasms with amlodipine (up to 10 mg daily), gabapentin (300-900 mg daily), pregabalin (varies with symptoms and causes), or cyclobenzaprine (5-10 mg 3 times daily) have been reported [33]. Nausea and vomiting might be treated with scopolamine given transdermally at 1.5 mg every 3 days as has been previously reported [33].

Conclusions and Summary

The approval of hedgehog pathway inhibitors for the treatment of laBCC and mBCC has changed the treatment landscape for patients with these cancers. As advanced BCC often occurs on visible parts of the body, concerns about appearance may adversely affect the QoL for these patients. Results from the ERIVANCE, STEVIE, and BOLT trials led to 2 hedgehog inhibitors, vismodegib and sonidegib, gaining approval in the United States (ERIVANCE and BOLT), Europe (ERIVANCE, STEVIE, and BOLT), Switzerland (ERIVANCE and BOLT), and Australia (ERIVANCE and BOLT).

Changes in QoL from baseline in the ERIVANCE, STEVIE, and BOLT trials ranged from no change to improvements in several domains [20,22,23]. Although the AE profile of hedgehog pathway inhibitors has fewer high-grade events compared with other targeted therapies, their impact on QoL should not be discounted due to their potentially chronic and bothersome nature. More effective management of AEs should help improve QoL for those patients with advanced BCC who often have AE-related decreases in QoL during their course of treatment.

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