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Quality of Life in Advanced Basal Cell Carcinoma and Treatment with Hedgehog Inhibitors

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ABSTRACT

Basal cell carcinoma (BCC) is the most common form of cancer, affecting approximately 2 million people in the United States annually. Abnormal activation of hedgehog signaling plays an important role in BCC. Two inhibitors of the Smoothened (SMO) component of the hedgehog pathway, vismodegib and sonidegib, are currently approved for use in advanced BCC (locally advanced BCC and metastatic BCC), 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. The key clinical trials for vismodegib (ERIVANCE and STEVIE) and for sonidegib (BOLT) included QoL as secondary end points. In ERIVANCE, the Short Form-36 showed no changes from baseline on either the physical or emotional domains. In STEVIE, the Skindex-16 showed that treatment with vismodegib was associated with clinically meaningful improvement in the emotional domain. BOLT used predetermined subscales relevant to advanced skin cancer 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 that affect QoL during treatment of patients with advanced BCC include baseline QoL, having fewer comorbidities, 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; hedgehog inhibitor; quality of life; sonidegib; vismodegib

Abbreviations: AE: Adverse Event; BCC: Basal Cell Carcinoma; BCCNS: BCC-Nevus Syndrome; BL: Baseline; CES-D: Center for Epidemiological Studies Depression Scale; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: EORTC Quality of Life Questionnaire; EORTC H&N35: EORTC Quality of Life Module for Head and Neck Cancer; laBCC: Locally Advanced BCC; mBCC, metastatic BCC; MCS: Mental Component Score; mDOR: Median Duration of Response; PCS: Physical Component Score; PTCH1: Patched1; ORR: Objective Response Rate; QoL: Quality of Life; RECIST: Response Evaluation Criteria in Solid Tumors; SCC: Squamous Cell Carcinoma; SF-36: Short Form-36; SMO: Smoothened

INTRODUCTION

Nonmelanoma skin cancers—basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)—are the most common malignancies affecting light-skinned individuals worldwide, and the incidence is increasing. The highest rates of BCC are seen in Australia (>1000/100,000 person-years) [1]. BCC and SCC are associated with exposure to ultraviolet radiation from sunlight, and therefore most often occur on visible parts of the body, such as the head and neck.

Abnormal activation of the hedgehog signaling pathway plays an important role in BCC development. Dysregulated signaling by mutated components of hedgehog signaling, especially Patched1 (PTCH1) and Smoothened (SMO), lead to continual activation of this pathway [2,3]. Such constant signaling activity affects cellular proliferation, invasion, and survival, especially in BCC. Therefore, two inhibitors of the SMO component of hedgehog signaling, vismodegib and sonidegib, were developed and approved for use in advanced

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forms of BCC (locally advanced BCC [laBCC] and metastatic BCC [mBCC]), depending on the country of approval (sonidegib is approved for advanced BCC in Australia and Switzerland and for locally advanced BCC in the European Union and the United States) [2,3].

Since surgery is frequently used to treat BCC, cosmetic concerns may occur as a result of treatment, and these considerations may negatively affect the quality of life (QoL) of patients with BCC [4-6]. Patients with BCC-nevus syndrome (BCCNS) have multiple BCC lesions, odontogenic keratocysts, palmar or plantar pits, and other abnormalities. Patients with BCCNS had decreased overall QoL, as observed in a study of 32 patients who completed the Skindex-29 QoL survey and the Center for Epidemiological Studies Depression Scale (CES-D). Moreover, the study results showed that depressive symptoms were particularly prevalent, with 50% of patients with BCNS having significant depressive symptomatology [7].

Predictors of how treatment for BCC may affect QoL have been examined. In one study of 633 patients with BCC or SCC, the single biggest QoL predictor post-treatment was the skin-related QoL prior to treatment versus post-treatment: for skin-related QoL, a 20-point difference between the prior to and after treatment score would indicate that clinically meaningful improvement in QoL had occurred as a result of treatment [8]. In a second study of 633 patients with BCC or SCC, QoL outcomes were similar after two common treatment modalities, Mohs surgery and excision [9]. Fewer comorbidities and better mental health status were independent predictors as well; however, tumor characteristics (histological type, location on head or neck, tumor diameter, noted histological risk factors for recurrence) were not predictors of QoL [10]. Moreover, patients with minimal clinical involvement may still be highly distressed, highlighting the patient-dependent variation in QoL associated with BCC and its treatment [10]. The goal of this brief review is to discuss the current literature on QoL regarding hedgehog inhibitors for advanced forms of BCC, with emphasis on trial data.

Assessing QoL in the ERIVANCE, STEVIE, and BOLT Trials

Vismodegib and sonidegib were approved based on results from randomized, multicenter trials, ERIVANCE (NCT00833417), STEVIE (NCT01367665), and BOLT (NCT01327053) [11-13]. All three trials included QoL as secondary end points but differed in the questionnaires used. In ERIVANCE, QoL was assessed (at baseline, week 12, week 24, and end of study) by changes from baseline on the Short Form (SF)-36 questionnaire, which recorded responses to 36 questions across 8 domains [14]. In STEVIE, the Skindex-16 questionnaire was used to assess how often patients were troubled by different aspects of their disease [10]. In BOLT, QoL was measured (at baseline, and every 12 weeks throughout the study) using relevant predetermined subscales of the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) and the EORTC H&N35 (EORTC Quality of Life Module for Head and Neck Cancer) [15,16]. The QoL instruments used in ERIVANCE, STEVIE, and BOLT differed in their assessments of the impact treatment would have on patients with BCC (**Table 1).** Only BOLT used questionnaires specific for patients with cancer.

QoL from the ERIVANCE Trial

ERIVANCE, the pivotal study on which approval for vismodegib was based in the United States, was a phase 2, multicenter, randomized trial. End points in ERIVANCE were evaluated by investigators and also by an independent, central review committee (first 12 months solely). Patients in ERIVANCE were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, as assessed by computed tomography or magnetic resonance imaging [17]. This single-arm, 2-cohort study had 104 patients with advanced BCC enrolled. Of these, 71 had laBCC and the remainder had mBCC. The objective response rates (ORR; primary end point) were 43% for patients with laBCC and 30% for patients with mBCC. By central review, the median duration of response (mDOR) was 7.6 months (range, 1.0–12.9) for patients with laBCC and 7.6 months (range, 2.1–11.1) for patients with mBCC [17]. Treatment-associated adverse events (AEs) included muscle spasms, alopecia, and dysgeusia. Most AEs were grade 1-2 [17].

ERIVANCE measured changes in QoL at baseline, weeks 12 and 24, and end of study or termination. Changes in QoL were assessed by changes from baseline on the Short Form (SF)-36 questionnaire, as one of its secondary end points [18]. This single-page questionnaire poses 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 (**Table 1).** A higher positive score on the SF-36 indicated better QoL [14]. The SF-36 was not designed to assess the QoL associated with skin disease but is a general assessment of QoL. At the end of the ERIVANCE study, patients maintained QoL as shown by the physical and emotional portions of the SF-36 (**Table 2)** [18].

QoL from the STEVIE Trial

STEVIE was an open-label, multicenter, postapproval trial for vismodegib having the largest enrollment of patients with advanced BCC at the time: 499 patients with laBCC and 31 with mBCC. End points in STEVIE were evaluated by investigators only, and not by a central review committee [19].

Table 1. Quality of Life Questionnaires Used for Patients with Advanced BCC in ERIVANCE, STEVIE, and BOLT

Trial	Reference(s)	Questionnaire(s)	Comments
ERIVANCE	[18]	SF-36	SF-36 physical component subscales: physical functioning, role−physical, bodily pain, and general health; mental component subscales: vitality, social functioning, role−emotional, and mental health.
STEVIE	[10]	Skindex-16	16 questions across 3 categories: symptoms (4 items), emotions (7 items), and functioning (5 items), each question assessing how often the patient is bothered by each.
BOLT	[22,23]	• EORTC QLQ-C30	• EORTC QLQ-C30 prespecified subscales: social functioning, physical functioning, pain, fatigue
		• EORTC H&N35	• EORTC H&N35 prespecified subscales used: trouble with social contact, head and neck pain, weight loss

BCC, basal cell carcinoma; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC H&N35, EORTC Quality of Life Module for Head and Neck Cancer; QoL, quality of life; SF-36, Short Form-36

Table 2. Quality of Life Results from SF-36 for Patients with Advanced BCC from ERIVANCE

	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 to 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

BCC, basal cell carcinoma; EOS, end of study; MCS, mental component score; PCS, physical component score; QoL, quality of life; SF-36, Short Form-36

Source: Data from the ERIVANCE trial data, NCT00833417, available at https://clinicaltrials.gov; retrieved January 25, 2018.

After 12 months, the primary end point was evaluated (percentage of participants who experienced any AEs, grade 3 or 4 AEs, AEs leading to drug interruptions or discontinuations, or any serious AEs) [12]. Regarding efficacy, STEVIE showed that 302 patients with laBCC had a response, of whom 153 had a complete response. Of 31 patients with mBCC, 11 had a complete response. Treatment-emergent AEs were frequent, occurring in 98% of patients who had <12 months exposure and in 99% of patients who had ≥12 months exposure. The most common of the latter were muscle spasms, alopecia, dysgeusia, and weight loss [12].

Results from the Skindex-16 questionnaire from STEVIE (**Table 3**) showed that patients given vismodegib had clinically meaningful improvement in the emotional domain [12,20,21]. There were slight improvements noted in the functional and symptom domains, of which only the improvement in the emotion scores were consistent with clinical responses (**Table 3**) [20].

QoL from the BOLT Trial

BOLT differed from ERIVANCE and STEVIE in evaluating response to treatment in that investigator as well as central review assessments were used throughout the 42-month trial duration. More stringent RECIST (BCC-modified RECIST; BCC-mRECIST) criteria were used to evaluate patients in BOLT than were used in ERIVANCE or STEVIE [22]. BCC-mRECIST is a multimodal tumor assessment method integrating magnetic resonance imaging per RECIST v1.1, standard and annotated color photography per World Health Organization guidelines, and histology in multiple biopsy specimens surveying the lesion area. Partial responses required a ≥30% decrease in the sum of the longest

diameters of target lesion(s) per RECIST v1.1 (imaging assessments) and a ≥50% reduction in the sum of the products of perpendicular diameters of target lesion(s) per WHO guidelines. Complete responses required total resolution of all lesions confirmed on repeated assessments ≥4 weeks apart by all modalities, and negative histological results [22]. Had less stringent response criteria been used in BOLT, the complete response rates would have been similar to those reported in ERIVANCE [13].

Table 3. Quality of Life Results for Patients with Advanced BCC from STEVIE

	Median Change from Baseline at End of Study		
	Domain in Skindex-16		
Subgroup	**Emotion**	**Symptom**	**Function**
All patients with laBCC	-23.8	-4.2	0
Sex			
Female	-29.8	-8.3	0
Male	-23.8	0	-3.3
Age			
18-40 yr	-14.3	0	-6.7
41-65 yr	-28.6	-8.3	-3.3
>65 yr	-21.4	-8.3	0
BCCNS			
Yes	-14.3	-4.2	-1.7
No	-28.6	-4.2	0
Location of lesions			
Head/neck	-23.8	-4.7	0
Other	-32.1	-10.4	-3.3

Data from [20] BCC, basal cell carcinoma; BCCNS, BCC-nevus syndrome; laBCC, locally advanced BCC

In BOLT, 230 patients were treated after randomization to two doses of sonidegib, 200 mg or 800 mg given once per day. At 30 months in patients with laBCC, the 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. By central review, mDOR was 26.1 months for patients with laBCC and 24.0 months for patients with mBCC [13]. These were longer than the mDOR seen for vismodegib in ERIVANCE (7.6 months for both laBCC and mBCC) [17].

Data from the 30-month analysis of BOLT in patients with mBCC showed 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 [13]. 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%]) [13].

QoL in BOLT was monitored at baseline, every 12 weeks, and at the 18-month prespecified end point. At 12 months, 82% of patients were still responding to sonidegib, the median duration of response had not yet been reached, and the majority of patients had maintenance of or improvement in predetermined subscale scores on the EORTC QLQ-C30 and the EORTC H&N35. Improvements in QLQ-C30 and H&N35 were found to be consistent across laBCC and mBCC cohorts (**Table 4**). This analysis showed >80% of patients reported maintenance or improvement in each predetermined subscale through week 73 (**Table 4**) [22-24]. The results of the EORTC H&N35 showed the most improvement in the domain of trouble with social contact, an indication that sonidegib may have improved some patients' concerns regarding the effect of advanced BCC on their appearance (**Table 4**).

Table 4. Quality of Life Results for Patients with Advanced BCC from BOLT

	Sonidegib 200 mg QD		**Sonidegib 800 mg QD**	
EORTC QLQ-C30	**laBCC**	**mBCC**	**laBCC**	**mBCC**
Physical functioning	n=61	n=13	n=110	n=20
• **Improvement from BL, n (%)**	22 (36)	9 (69)	35 (32)	8 (40)
• **No change from BL, n (%)**	29 (48)	3 (23)	38 (35)	10 (50)
• **Decline from BL, n (%)**	10 (16)	1 (8)	37 (34)	2 (10)
Social functioning	n=61	n=13	n=109	n=20
• **Improvement from BL, n (%)**	16 (26)	5 (39)	22 (20)	7 (35)
• **No change from BL, n (%)**	40 (66)	6 (46)	75 (69)	12 (60)
• **Decline from BL, n (%)**	5 (8)	2 (15)	12 (11)	1 (5)
Pain	n=61	n=13	n=110	n=20
• **Improvement from BL, n (%)**	19 (31)	6 (46)	36 (33)	11 (55)
• **No change from BL, n (%)**	36 (59)	7 (54)	52 (47)	7 (35)
• **Decline from BL, n (%)**	6 (10)	0	22 (20)	2 (10)
Fatigue	n=61	n=13	n=109	n=20
• **Improvement from BL, n (%)**	23 (38)	6 (46)	21 (19)	8 (40)
• **No change from BL, n (%)**	26 (43)	6 (46)	55 (51)	8 (40)
• **Decline from BL, n (%)**	12 (20)	1 (8)	33 (30)	4 (20)
EORTC H&N35				
Trouble with social contact	n=58	n=13	n=110	n=19
• **Improvement from BL, n (%)**	25 (43)	4 (31)	33 (30)	8 (42)
• **No change from BL, n (%)**	27 (47)	7 (54)	68 (62)	9 (47)
• **Decline from BL, n (%)**	6 (10)	2 (15)	9 (8)	2 (11)
Head and neck pain	n=60	n=13	n=112	n=20
• **Improvement from BL, n (%)**	11 (18)	3 (23)	20 (18)	4 (20)
• **No change from BL, n (%)**	47 (78)	9 (69)	78 (70)	12 (60)
• **Decline from BL, n (%)**	2 (3)	1 (8)	14 (13)	4 (20)
Weight loss	n=58	n=12	n=110	n=19
• **Improvement from BL, n (%)**	9 (16)	2 (17)	8 (7)	5 (26)
• **No change from BL, n (%)**	49 (85)	8 (67)	89 (81)	14 (74)
• **Decline from BL, n (%)**	0	2 (17)	13 (12)	0

Data from [22]. BCC, basal cell carcinoma; BL, baseline; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC H&N35, EORTC Quality of Life Module for Head and Neck Cancer; laBCC, locally advanced BCC; mBCC, metastatic BCC; QoL, quality of life

RECIST vs BCC-mRECIST

Patients with laBCC in ERIVANCE were evaluated using a composite end point: a decrease of ≥30% in the externally visible or radiographic dimension or complete resolution of ulceration, if present at baseline [17].

In BOLT, more stringent RECIST criteria were used to evaluate patients with laBCC. BCC-modified RECIST (BCC-mRECIST) is a multimodal tumor assessment method integrating magnetic resonance imaging (MRI) per RECIST v1.1, standard and annotated color photography per World Health Organization guidelines, and histology in multiple biopsy specimens surveying the lesion area. Partial response in lesions assessed by MRI required a ≥30% decrease in the sum of the longest diameters of target lesion(s) per RECIST v1.1 (imaging assessments) and in lesions assessed by photography, a ≥50% reduction in the sum of the products of perpendicular diameters of target lesion(s) per WHO guidelines. Complete responses required total resolution of all lesions confirmed on repeated assessments ≥4 weeks apart by all modalities, and all of multiple biopsies yielding negative histological results [22].

DISCUSSION

BCC affects QoL variably, depending upon stage of disease and symptoms. In a recent study of 34 patients with BCC (21 of whom had advanced BCC), 95% of patients with advanced BCC identified their symptoms as bothersome, compared with 69% of patients with BCC. Over three-quarters (76%) of patients with advanced BCC reported limiting their daily activities as a result of their disease, compared with 46% of patients with BCC. Furthermore, 57% of patients with advanced BCC reported limiting activities (eg, exposure to sun, or strenuous activities in part due to surgery), compared with 31% of patients with BCC [25].

Patients with BCCNS reported decreased QoL, and for these patients, depressive symptoms were more prevalent [7]. The impact of treatment for BCCNS was evaluated using the Skindex-29 in this study [7]. Patients with BCCNS are often treated with surgery; this study evaluated the extent to which multiple surgeries affected QoL. Investigators found that patients treated with surgery scored significantly lower on the CES-D scale for depressive symptoms than did patients not treated with surgery (lower scores on the CES-D scale indicate fewer depressive symptoms) [7]. In a second study, patients with BCCNS were compared with patients with advanced BCC. The investigators observed that patients with BCCNS had profiles similar to those of patients with chronic illness, whereas the profile of patients with advanced BCC resembled more closely patients with acute illnesses [26].

Nonsurgical, nonpharmaceutical treatment of BCC (radiation therapy) was shown to affect the QoL of patients with BCC. One study compared patients with BCC treated with X-ray therapy with healthy, matched individuals (25 in each cohort). The patients' Dermatology QoL Index decreased significantly, indicating improvement in scores, at 3 months following treatment and were similar to the scores of matched healthy control subjects. The subcategory most affected was Symptoms and Feelings, which showed a significant decline in score from baseline to 3 months after treatment [27]. It is interesting to note that the Daily Activities subcategory showed no significant change from baseline following therapy.

Finally, the impact of treatment-emergent AEs on QoL should be discussed. Unlike targeted therapies approved for other types of cancer (eg, sorafenib, imatinib), which can cause various cutaneous AEs (among them hypopigmentation, maculopapular rash, and epidermoid cysts) [28,29], alopecia is the main cutaneous AE resulting from treatment with hedgehog inhibitors [28]. Common noncutaneous AEs include muscle spasm, dysgeusia, fatigue, and nausea [11,22]. Moreover, although the majority of the AEs reported for vismodegib and sonidegib were grade 1-2, it should be noted that patients may take either of these drugs for a longer term [30,31], so managing AEs may lead to higher QoL and increased treatment effect, due to more consistent drug exposure. For example, diarrhea may be treated with loperamide 2 mg up to 16 mg daily, and alopecia may respond to 5% topical minoxidil twice daily [32].

CONCLUSIONS AND SUMMARY

The approval of two hedgehog inhibitors for laBCC and mBCC, vismodegib and sonidegib, changed the treatment paradigm for patients with advanced forms of BCC. The approvals were based on results from the ERIVANCE and STEVIE trials for vismodegib and the BOLT trial for sonidegib. Because advanced BCC most often occurs on the more visible parts of the body such as the head and neck, patients may be concerned about appearance, and these worries may adversely affect their QoL. Changes in QoL from baseline in the ERIVANCE, STEVIE, and BOLT trials ranged from no change to improvements in several domains [11,19,22]. Although the AE profiles of approved hedgehog inhibitors have fewer high-grade events compared with other targeted therapies, the impact of commonly occurring AEs on QoL should not be discounted due to their chronic and bothersome aspects, which may limit use of these therapies. More effective AE management should help improve QoL for patients with advanced BCC who are at risk of experiencing decreased QoL during their course of treatment.

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REFERENCES

1. Lomas A, Leonardi-Bee J, Bath-Hextall F (2012) A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 166: 1069-1080.

2. Peukert S, Miller-Moslin K (2010) Small-molecule inhibitors of the hedgehog signaling pathway as cancer therapeutics. Chem Med Chem 5: 500-512.

3. Zheng X, et al. (2013) Role of the hedgehog pathway in hepatocellular carcinoma (review). Oncol Rep 30: 2020-2026.

4. Philipp-Dormston WG, et al. (2017) Patient-reported health outcomes in patients with non-melanoma skin cancer and actinic keratosis: results from a large-scale observational study analysing effects of diagnoses and disease progression. J Eur Academy Dermatol Venereol. [in press]

5. Gaulin C, Sebaratnam DF, Fernández-Peñas P (2015) Quality of life in non-melanoma skin cancer. Aus J Dermatol 56: 70-76.

6. Lanoue J, Goldenberg G (2016) Basal cell carcinoma: a comprehensive review of existing and emerging nonsurgical therapies. J Clin Aesthetic Dermatol 9: 26-36.

7. Shah M, et al. (2011) Quality of life and depression assessment in nevoid basal cell carcinoma syndrome. Int J Dermatol 50: 268-276.

8. Chen T, et al. (2007) Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. Archives Dermatol 143: 1386-1392.

9. Chren MM, et al. (2007) Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. J Investigative Dermatol 127: 1351-1357.

10. Chren MM (2012) The Skindex instruments to measure the effects of skin disease on quality of life. Dermatologic Clinics 30: 231-236.

11. Sekulic A, et al. (2017) Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. BMC Cancer 17: 332.

12. Basset-Seguin N, et al. (2015) Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. Lancet Oncol 16: 729-736.

13. Lear JT, et al. (2018) Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT Study. J Eur Acad Dermatol Venereol. 32: 372-381.

14. Ware JE, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). Medical Care 30: 473-483.

15. Aaronson NK, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85: 365-376.

16. Bjordal K, et al. (1999) Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. J Clin Oncol 17: 1008-1019.

17. Sekulic A, et al. (2017) Long-term efficacy and safety of vismodegib in patients with advanced basal-cell carcinoma: final update of the pivotal ERIVANCE BCC Study. BMC Cancer 17: 332.

18. National Cancer Institute (2017) A study evaluating the efficacy and safety of vismodegib (GDC-0449, hedgehog pathway inhibitor) in patients with advanced basal cell carcinoma. Available from: https://clinicaltrials.gov/ct2/show/NCT00833417?term=NCT00833417&rank=1.

19. Basset-Seguin N, et al. (2017) Vismodegib in patients with advanced basal cell carcinoma: primary analysis of STEVIE, an international, open-label trial. Eur J Cancer 86: 334-348.

20. Hansson J, et al. (2015) 3342 Assessment of quality of life using Skindex-16 in patients with advanced basal cell carcinoma (BCC) treated with vismodegib in the STEVIE study. Eur J Cancer 51: S680-S681.

21. Grob JJ, et al. (2016) Assessment of quality of life (QoL) using Skindex-16 in patients (pts) with locally advanced basal cell carcinoma (laBCC) treated with vismodegib (VISMO) in the STEVIE study. J Am Academy Dermatol 74: AB193.

22. Migden MR, et al. (2015) Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. Lancet Oncol 16: 716-728.

23. Dummer R, et al. (2014) Patient-reported quality of life (QOL) with sonidegib (LDE225) in advanced basal cell carcinoma (BCC). Annals Oncol 25: iv390-iv390.

24. Guminski A, et al. (2014) Quality of life (QOL) in patients (pts) with advanced basal cell carcinoma (BCC) treated with sonidegib (LDE225). Pigment Cell Melanoma Res 27: 1195.

25. Steenrod AW, et al. (2015) A qualitative comparison of symptoms and impact of varying stages of basal cell carcinoma. Dermatol Therapy 5: 183-199.

26. Mathias SD, et al. (2014) Assessing health-related quality of life for advanced basal cell carcinoma and basal cell carcinoma nevus syndrome: development of the first disease-specific patient-reported outcome questionnaires. JAMA Dermatol 150: 169-176.

27. Skiveren J, et al. (2012) Skin reactions and quality of life after x-ray therapy of basal cell carcinoma. J Skin Cancer. 2012: 825095.

28. Tang N, Ratner D (2016) Managing cutaneous side effects from targeted molecular inhibitors for melanoma and nonmelanoma skin cancer. Dermatologic Surgery 42: S40-S48.

29. Tischer B, et al. (2017) Dermatologic events from EGFR inhibitors: the issue of the missing patient voice. Supportive Care Cancer 25: 651-660.

30. Genentech USA (2017) Erivedge prescribing information. South San Francisco, CA.

31. Sun Pharmaceuticals Industries, Ltd. (2017) Odomzo prescribing information. Cranbury, NJ.

32. Lacouture ME, et al. (2016) Characterization and management of hedgehog pathway inhibitor-related adverse events in patients with advanced basal cell carcinoma. The Oncologist 21: 1218-1229.