



Qualitative Patient Interviews to Characterize the Human Burden of Advanced Basal Cell Carcinoma Following Hedgehog Pathway Inhibitor Treatment

Gerasimos Konidaris · Diana Rofail · Jason Randall · Patrick R. LaFontaine · Chieh-I. Chen · Denise Bury · Ashley Geiger · Medha Sasane · Tara Symonds

Received: February 9, 2023 / Accepted: May 23, 2023 / Published online: June 17, 2023
© The Author(s) 2023

ABSTRACT

Introduction: Evidence of patients' experiences of living with advanced basal cell carcinoma (aBCC) are limited, particularly after hedgehog pathway inhibitor (HHI) treatment. We explored the burden of aBCC on symptoms and patients' everyday lives post HHI treatment.

Methods: In-depth, semi-structured, approximately 1-h qualitative interviews of US patients with aBCC and prior HHI treatment were conducted. Data were assessed using thematic analysis with NVivo 1.0 software. Saturation analysis was performed to ensure all concepts were captured.

Results: Fifteen patients (median age, 63 years; locally advanced BCC, $n = 9$; metastatic BCC, $n = 6$) were interviewed. A patient-led conceptual model was developed from the responses using 10 symptoms and 15 impact categories (comprising emotional/psychological, physical, and social domains) identified as most commonly discussed and important to patients. Overall, reported impacts were discussed more commonly than reported symptoms. Impacts most commonly discussed were related to emotions (e.g., anxiety, worry, fear [$n = 14$; 93%]; low mood, depression [$n = 12$; 80%]) and physical function (e.g., hobbies or leisure activities [$n = 13$; 87%]). Symptoms most commonly discussed were fatigue and tiredness ($n = 14$; 93%) and itch ($n = 13$; 87%). Out of all reported impacts and symptoms, fatigue and tiredness ($n = 7$, 47%) and anxiety, worry, and fear ($n = 6$; 40%) were most bothersome to patients. As a descriptive exercise, participant responses were mapped to commonly used patient-reported outcome scales in aBCC clinical trials. Most expressed concepts were captured across two common measures in oncology/skin conditions (European Organization for Research and Treatment of Cancer Quality of Life-Core 30 [EORTC QLQ-C30] and Skindex-16 questionnaires), but sun avoidance and others' perception of skin cancer were not explicitly mentioned by these instruments.

Conclusion: Patients with aBCC experienced a significant disease burden post first-line HHI

G. Konidaris
Sanofi, Reading, UK

D. Rofail · C.-I. Chen
Regeneron Pharmaceuticals, Inc., Tarrytown, NY,
USA

J. Randall · T. Symonds
Clinical Outcomes Solutions Ltd, Folkestone, Kent,
UK

P. R. LaFontaine (✉) · D. Bury · M. Sasane
Sanofi, Cambridge, MA, USA
e-mail: patrick.lafontaine@sanofi.com

A. Geiger
IQVIA, Mesa, AZ, USA

Present Address:
D. Bury
Novartis, Cambridge, MA, USA

therapy, including major emotional and lifestyle impacts. Accordingly, through this study, patients with aBCC highlighted a significant unmet need for second-line treatment options post HHI therapy.

Keywords: Advanced basal cell carcinoma; Patient-reported outcomes; Post-hedgehog inhibitor treatment; Qualitative research; Quality of life; Symptoms and impacts

Key Summary Points

Why carry out this study?

Qualitative literature on the direct experience of patients with advanced basal cell carcinoma (aBCC) who discontinue first-line treatment with a hedgehog pathway inhibitor (HHI) is sparse.

To better understand the patient experience, this study aimed to identify the reported symptoms and impacts on health-related quality of life (HRQoL) that are most important to patients with aBCC who were previously treated with an HHI.

What was learned from the study?

Patients described a significant disease burden in aBCC, even after previous treatment with an HHI. The most commonly discussed concepts were fatigue and tiredness, itch, anxiety, worry, and fear, such as day-to-day anxiety and fear about the future. Of these, fatigue and tiredness, anxiety, worry, and fear were considered the most bothersome concepts.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common form of non-melanoma (keratinocyte) skin cancer in the USA, with approximately 3.6 million cases and more than 3000 deaths per

year [1]. In 2017, the global incidence of reported BCC was 5,884,759 cases, reflecting a 77.4% increase in new diagnoses between 1990 and 2017 [2].

Surgical excision, when possible, is the standard treatment of BCC. However, inadequate or incomplete excision increases the risk of recurrence, and such tumors may require re-excision [3–5]. Fewer than 1% of cases progress to locally advanced or metastatic disease, collectively referred to as advanced BCC (aBCC) [6], and may consequently require systemic therapy [7]. European Medicines Agency (EMA) and US Food and Drug Administration (FDA)-approved and guideline-recommended therapies that target the hedgehog signaling pathway (hedgehog pathway inhibitors, HHIs) have been used as a first-line systemic therapy against aBCC not amenable to curative surgery or radiotherapy. Eventual discontinuation of first-line HHI therapy is common because of progression of disease or adverse events [3–5, 8–14]. In 2021, the FDA and EMA approved the use of cemiplimab, a programmed cell death-1 inhibitor, for the treatment of patients with aBCC previously treated with an HHI or for whom an HHI is not appropriate [15].

Qualitative literature is sparse on the experience of aBCC from the patient perspective. Shingler et al. [16] explored the psychological and cosmetic burden to patients with aBCC by constructing a series of health state vignettes based on clinician input. Mathias et al. [17, 18] developed a patient-reported outcome (PRO) questionnaire describing BCC-related impacts, stratified by basal cell nevus syndrome versus aBCC. However, these methods did not provide patients the opportunity to describe how they experienced their disease in their own words. Steenrod et al. [19] conducted qualitative interviews with patients with BCC and identified high-level information on symptoms and impacts, but this work did not develop a more detailed understanding of the lived experience of patients with this condition, and less than a third of patients included had previous exposure to HHI therapy.

There are a few validated PRO scales that characterize the complex burden of oncologic skin conditions. These include the European

Organization for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30) questionnaire, a health-related quality of life (HRQoL) measure developed for patients with cancer that assesses a range of physical limitations and mood [20], and the Skindex-16 questionnaire which was developed and validated to assess HRQoL in patients with BCC and cutaneous squamous cell carcinoma [21]. The EORTC QLQ-C30—the most commonly utilized instrument to assess HRQoL in patients with skin cancer [22]—and the Skindex-16 questionnaire provide valuable indicators of the impact of disease on symptoms, functioning, and quality of life, despite limiting the patient to a set of predefined questions that may not completely correspond with their experiences with aBCC. Although the EORTC QLQ-C30 and Skindex-16 questionnaires were previously included in BCC clinical trials [23, 24], the Skindex-16 questionnaire was not previously used to assess HRQoL in patients with aBCC post first-line HHI therapy.

The objective of this study, which is based on constructivist principles, was to capture, through semi-structured qualitative interviews, the specific symptoms and impacts on HRQoL that are most important to patients with aBCC who previously received HHI therapy and develop a conceptual model to better understand the patient experience.

METHODS

This study was conducted in compliance with Good Clinical Practice guidelines, including the International Conference on Harmonization guidelines, and was consistent with the most recent version of the Declaration of Helsinki [25]. All applicable local laws and regulatory requirements were followed throughout the study.

Study Design

In-depth semi-structured interviews were conducted with US patients with metastatic or locally advanced BCC. The interviews were initially planned to be face-to-face but were

replaced with telephone interviews owing to the severe acute respiratory syndrome coronavirus 2 (COVID-19) pandemic. To facilitate the opportunity for patients to mention concepts spontaneously, a discussion guide was developed based on informal literature searches [1, 19, 26–28] and the researchers' experience with qualitative research and clinical outcome assessment research. The discussion guide was developed so that interviewers could maintain a level of consistency between patient interviews and ensure that all key topics were adequately covered. The discussion guide comprised of four sections: (1) the "overview of the interview" which stated the objective and schedule, (2) the "interview instructions" for the person conducting the interview, (3) the "introduction" where objectives and disclosures were discussed with the participant, and (4) the "interview" where concept elicitation took place, and the interview was concluded. Interviews were designed to last approximately 60 min and were conducted by two trained qualitative researchers who had substantial experience conducting qualitative interviews across numerous studies, including oncology. The interviewers received project-specific training to ensure that they were familiar with the project objectives, discussion guide, and disease area, including mock interviews prior to speaking with patients. To ascertain unbiased responses and encourage spontaneous discussion, interviewers were specifically instructed per the discussion guide to use open-ended questions, and use probes to follow-up without inadvertently leading a participant's response. A list of example interview questions is provided in Table 1. Interviews were designed to be exploratory and semi-structured to allow for an in-depth understanding of individual experiences in living with metastatic or locally advanced BCC post HHI treatment. Specifically, semi-structured interviews allowed for the investigation of thoughts, experiences, and details volunteered by the participants that would not be possible with structured interviews [29].

Interviews proceeded as follows: brief initial questions designed to establish rapport and open the conversation (e.g., "Could you tell me what symptoms you are experiencing now,

Table 1 Example interview questions

-
1. Could you tell me what symptoms you are experiencing NOW, relating to your [BCC]?
How long has this symptom been present?
Is this symptom important to you?
When did you notice this?
How else would you describe that feeling? What other words would you use to talk about it?
Where on/in your body do you experience this? Are there any other areas you get this? (verbalize location for recording)
How severe is it? Could you rate it from 0 to 10 (where 0 is not bad at all and 10 is the worst possibly it could be)?
 2. Thinking about how your [BCC] is NOW, can you tell me if it ever makes anything difficult to do, or prevents you from doing anything?
 3. We would like to understand any other experiences you have had in terms of symptoms or how living with [BCC] affects your daily life. What we would like to do now is go through some other areas to see if there are things you are currently experiencing relating to your [BCC]? Some people with [BCC] experience [concept from table not previously mentioned], is this something that you have experienced due to your [BCC]?
 4. Thinking about all of the topics we have discussed relating to your [BCC], which would you say are the three most important to you?
-

BCC basal cell carcinoma

related to your BCC? Thinking about how your BCC is now, can you tell me if it ever makes anything difficult to do, or prevents you from doing anything?”), a series of focused questions to explore topics of interest (e.g., “We would like to understand any other experiences you have had in terms of symptoms or how living with BCC affects your daily life. What we would like to do now is go through some other areas to see if there are things you are currently experiencing relating to your BCC”), probes to explore relevant issues not previously mentioned in the interview (e.g., “Some people with BCC experience [concept from table not previously mentioned]. Is this something that you have experienced due to your BCC?”), and a request for participants to rank the three most bothersome symptoms and impacts that had been discussed in the interview (e.g., “Thinking about all of the topics we have discussed relating to your BCC, which would you say are the three most important to you?”). All interviews were recorded and transcribed verbatim. All data were analyzed using thematic analysis. No

therapeutic interventions or treatments were administered as part of this study.

Patient Selection Criteria

Patients were eligible for study enrollment if they had a clinical diagnosis of aBCC, prior HHI treatment, and met the inclusion criteria, as assessed by the treating physicians. Key inclusion criteria were age 18 years or older; ability to understand informed consent and to participate in the interview; being unlikely to benefit further from HHI treatment because of disease progression, treatment intolerance, or stable response while undergoing HHI treatment; and being treatment-naïve following the cessation of HHIs. Key exclusion criteria included eligibility of their BCC for curative surgery or curative radiotherapy, clinical diagnosis of cutaneous squamous cell carcinoma, untreated brain metastases, chronic drug or alcohol abuse, or significant uncontrolled psychiatric or physical comorbidities that would impact the ability of patients to participate in this study.

Recruitment

Recruitment was conducted through an agency that contacted oncologists to identify individuals who met the study eligibility criteria under a Health Insurance Portability and Accountability Act waiver. Prior to any study-related procedure, eligible patients who agreed to participate provided a signed and dated fully informed consent form and an Authorization to Use and Disclose Personal Health Information Form. Upon recruitment, the treating clinicians completed an Eligibility Assessment Form to screen each participating patient based on the inclusion and exclusion criteria. For each eligible participant, the treating clinicians completed a brief Medical History Form to document date of aBCC diagnosis, date of HHI therapy discontinuation, characterization of the patient's disease as metastatic or local BCC, as well as a current and previous history of treatments with dosages, treatment/symptom target (e.g., pain reduction), treatment start date, and response to treatment. The clinicians worked with the participants to complete a Demographic Health Information Form that listed gender, ethnicity, race, education, and employment status.

Target quotas were used to obtain diverse representation of age, sex, ethnicity, education, metastatic versus locally advanced status, and length of time post HHI treatment. The minimum target quotas, which were intended to provide a broad representation of the second-line eligible aBCC patient population, included six patients of greater than 65 years of age, six men, four women, two patients who identified as Hispanic, two patients with a high school diploma as the highest level of education, two patients with metastatic BCC, eight patients with locally advanced BCC, and seven patients at least 6 months beyond the cessation of first-line HHI treatment.

Analysis

Transcripts of the interviews were entered into NVivo 10 (updated to NVivo 1.0 during analysis), a software package designed to facilitate the

storage, coding, and analysis of qualitative data [30]. Thematic analysis is a well-accepted and widely used approach for interpreting qualitative data [31] that uses both inductive and deductive coding and was considered the most suitable methodology for the present study. In thematic analysis, line-by-line coding is used to identify meaning in the transcripts and to identify any themes, patterns, or features of interest within the data relating to the research aims. The initial pass of the data focused on inductive coding methods which were then followed up using a deductive approach.

The data were also subjected to concept saturation analysis [32], which was undertaken by splitting the study sample into three equal groups of five based on the order in which they were interviewed. If a concept was discussed spontaneously or endorsed after probing by at least one patient within a group, it was noted as having been raised as relevant within that specific group. Concept saturation was considered met when no new themes or descriptions of concepts were identified in the final group of interviews.

Following coding, the signs, symptoms, and impacts reported by patients during the interviews were used to generate a patient-led conceptual model [33, 34]. The conceptual model was a visual representation of aspects of patients' experience living with aBCC. Impacts reported by patients were categorized into emotional/psychological, physical, and social domains. As an exploratory and deductive exercise, concepts covered by the EORTC QLQ-C30 [20] and Skindex-16 [21] questionnaires, two widely used measures in oncology and skin condition clinical trials, were mapped to those identified during the interviews to descriptively assess the adequacy of the concept coverage of these PRO measures in assessing the burden of aBCC.

RESULTS

Patient Characteristics

The quotas for age, gender, ethnicity, education, and condition status were all met or

exceeded during the study. However, the target quota ($n = 7$) for participants at least 6 months beyond cessation of HHI therapy was met by only two patients. This in part was due to recruitment delays associated with the COVID-19 pandemic, and recruiters were unable to identify sufficient patients to meet this quota. After the recruitment of the first ten participating patients, feedback from the recruiter was reviewed, and the study team agreed that this quota could be removed.

There were 15 participants enrolled in the study with a median age (range) of 63 (38–73) years. Most participants identified as White race (66.7%) and non-Hispanic/Latino ethnicity (73.3%) and were predominantly female (60%) (Table 2). Sixty percent of participants had locally advanced BCC and 40% had metastatic BCC. Median (range) time since initial diagnosis of BCC was 10.1 (4.1–61.2) months, the median (range) time from initial BCC diagnosis to aBCC diagnosis was 6.8 (0.3–56.4) months, and median (range) time since cessation of HHI treatment was 2.8 (0.7–9.1) months (Table 2). All participants had received previous HHI treatment, most commonly sonidegib ($n = 10$), and 12 patients reported prior Mohs surgery. No other treatments were reported. No differences were seen in the data between any of the compared subgroups (sex, race, ethnicity, or clinical status).

Main Findings

Concept saturation for reported signs, symptoms, and impacts were considered met, with no new concepts identified in the final round of five interviews. A patient-centered conceptual model was developed based on ten reported symptoms and 15 reported impact categories (divided into emotional/psychological, social, and physical domains) that were most commonly discussed and considered important to patients (Fig. 1). Four concepts were each discussed by only one participant, namely vomiting, difficulties with memory, feeling generally ill, and financial difficulties. These concepts were thematically determined to not be core concepts and were subsequently excluded in the

Table 2 Patient demographics and baseline characteristics

Demographic variables	Total ($N = 15$)
Age, years, median (range)	63.0 (38.0–73.0)
Age, years, mean (SD)	56.7 (12.1)
Male, n (%)	6 (40.0)
Race, n (%)	
White	10 (66.7)
Black/African American	1 (6.7)
Asian	0
American Indian/Alaska Native	1 (6.7)
Native Hawaiian/Pacific Islander	0
Other (Hispanic)	3 (20.0)
Hispanic/Latino, n (%)	4 (26.7)
Non-Hispanic/Latino, n (%)	11 (73.3)
Education, n (%)	
Did not complete high school	0
High school diploma	3 (20.0)
Some college or certification program	5 (33.3)
College or university degree	5 (33.3)
Graduate degree	2 (13.3)
Clinical variables	
Months since BCC diagnosis	
Median (range)	10.1 (4.1–61.2)
Mean (SD)	19.9 (19.5)
Months since discontinuation of HHIs	
Median (range)	2.8 (0.7–9.1)
Mean (SD)	3.1 (2.2)
Months from BCC diagnosis to aBCC diagnosis	
Median (range)	6.8 (0.3–56.4)
Mean (SD)	16.7 (17.9)
Metastatic, n (%)	6 (40.0)
Locally advanced, n (%)	9 (60.0)
Previous treatments, n of patients	
Mohs surgery	12
Sonidegib	10

Table 2 continued

Demographic variables	Total (N = 15)
Vismodegib	5
Duration of sonidegib treatment, months	
Median (range)	9 (3–17)
Mean (SD)	6 (4.6)
Duration of vismodegib treatment, months	
Median (range)	4 (1–6)
Mean (SD)	3.4 (1.7)

aBCC advanced basal cell carcinoma, BCC basal cell carcinoma, HHI hedgehog pathway inhibitor, SD standard deviation

conceptual model. For all concepts, no clear qualitative differences could be discerned across any subgroup (sex, ethnicity, or metastatic versus locally advanced BCC).

Patient-Reported Symptoms

The most commonly discussed symptom, reported by all but one participant (n = 14; 93%), was fatigue and tiredness (Table 3). This symptom was reported spontaneously by 12 participants, with an additional two

participants reporting it after some probing. Various terms were used by participants to describe their fatigue and tiredness, including “lack of energy” (n = 9) and “mentally and physically exhausted” (n = 7). One participant commented, “Saying tired, that’s putting it a little mildly. I would say it’s an exhaustion. I feel like I’m exhausted. Sometimes I wake up and I feel like I didn’t sleep.” Fatigue and tiredness were classified as important by 12 of the 14 participants, with one participant stating, “It’s important, ‘cause there’s so much that I wanna do but my body just won’t let me do it.” The remaining two participants indicated it was not important and had little impact on their day-to-day life, e.g., “[Fatigue and tiredness] doesn’t bother me. It’s not severe enough to bother me right now.” Consistency of fatigue and tiredness was discussed by 12 participants, and results varied; six participants described feelings of tiredness as generally constant, and six spoke about how it was more variable. Feelings of fatigue and tiredness were considered to impact other aspects of their day-to-day lives, including sleep (n = 7), social interactions and activities (n = 5), household tasks (n = 4), and personal hobbies and activities (n = 4).

Itch was the second most commonly discussed symptom of aBCC (n = 13; 87%), arising spontaneously in discussion with 11 participants, and after probing with an additional two participants. The location of the itch was

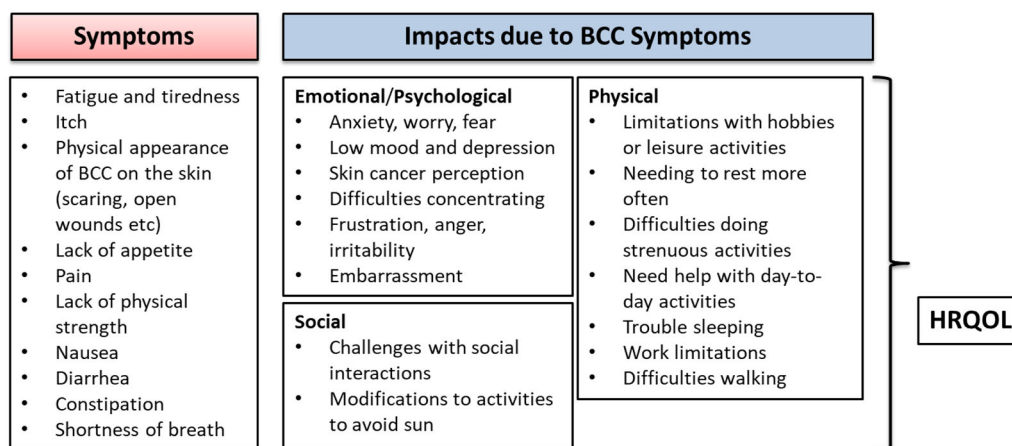


Fig. 1 Patient-centered conceptual model of aBCC after first-line HHI therapy discontinuation. BCC basal cell carcinoma, HRQoL health-related quality of life

Table 3 Reported symptoms and areas of impact

Concept	Sub-concept	Total patients mentioning (%)	First mention, spontaneous, <i>n</i>	Reported when probed, <i>n</i>
Symptoms	Fatigue and tiredness	14 (93)	12	2
	Itch	13 (87)	11	2
	Physical appearance of BCC on skin	9 (60)	5	4
	Lack of appetite	8 (53)	0	8
	Pain	7 (47)	5	2
	Lack of physical strength	5 (33)	5	0
	Nausea	4 (27)	1	3
	Diarrhea	4 (27)	1	3
	Constipation	2 (13)	0	2
	Shortness of breath	2 (13)	0	2
	Vomiting	1 (7)	0	1
	Difficulty with memory	1 (7)	0	1
	Feeling generally ill	1 (7)	1	0
Physical impacts	Limitations with hobbies or leisure activities	13 (87)	9	4
	Needing to rest more often	10 (67)	1	9
	Difficulties doing strenuous activities	9 (60)	2	7
	Need help with day-to-day activities	8 (53)	5	3
	Trouble sleeping (staying asleep and going to sleep)	8 (53)	2	6
	Work limitations	4 (27)	1	3
	Difficulties walking	3 (20)	0	3
Emotional/ psychological impacts	Anxiety, worry, fear	14 (93)	13	1
	Low mood or depression	12 (80)	6	6
	Perception by others of skin cancer	9 (60)	4	5
	Difficulties concentrating	8 (53)	2	6
	Frustration, anger, irritability	8 (53)	4	4
	Embarrassment	7 (47)	4	3

Table 3 continued

Concept	Sub-concept	Total patients mentioning (%)	First mention, spontaneous, <i>n</i>	Reported when probed, <i>n</i>
Social impacts	Challenges with social interactions	8 (53)	5	3
	Modifications to activities to avoid sun	7 (47)	7	0
Other	Financial difficulties due to skin condition	1 (7)	0	1

BCC basal cell carcinoma

dependent on the location of the participant's BCC, with the most common locations being the back ($n = 5$) and neck ($n = 4$). Itch was described as important to their experience of the condition by nine of the 13 participants, and those who described it as unimportant stated it was not important at the moment, or that it was not currently bothersome. As with fatigue and tiredness, the consistency of itch also varied between participants, with five participants describing their itch as constant, and seven as more variable.

Less commonly discussed symptoms included the physical appearance of BCC on the skin (scarring, open wound, etc.; $n = 9$; 60%), lack of appetite ($n = 8$; 53%), pain ($n = 7$; 47%), lack of physical strength ($n = 5$; 33%), nausea ($n = 4$; 27%), diarrhea ($n = 4$; 27%), constipation ($n = 2$; 13%), and shortness of breath ($n = 2$; 13%) (Table 3).

Patient-Reported Impacts

Impacts were more commonly discussed by participants than symptoms. Anxiety, worry, or fear were discussed by all but one of the enrolled participants ($n = 14$; 93%), 13 spontaneously and one after probing. These three emotional impacts were grouped based on participant feedback on similar concepts that captured different aspects of the same feelings. Most participants ($n = 11$; 73%) discussed being worried, anxious, and afraid about the future, with 5

(33%) feeling generally anxious from day to day. One participant described the emotional impact of BCC, "[My BCC] gives me a lot of anxiety, I would, I would say... Just because I know at this point that it has locally advanced in the same region. Um, and there's nothing that we can do about it right now, or ever, at this point."

The second most common reported emotional impact was low mood or depression related to aBCC ($n = 12$; 80%). This was discussed spontaneously by six participants and by the remaining six participants after probing. All participants who reported emotional impact identified it as important to them, and six described it as intermittent based on the reported symptoms they were experiencing at any given time. Terms used to describe these feelings included "emotional," "emotional wreck," and "feeling vulnerable and worthless." Emotional impacts, which were less commonly reported, included skin cancer perception by others ($n = 9$; 60%), difficulties concentrating ($n = 8$; 53%), frustration, anger, and irritability ($n = 8$; 53%), and embarrassment ($n = 7$; 47%).

The most discussed physical impact of aBCC was the limitation of hobbies or leisure activities. Thirteen participants discussed this concept, nine spontaneously and four after probing. Fatigue and tiredness was found to impact the hobbies or leisure activities of four participants, and two identified a lack of

physical strength as the symptom causing this impact, e.g., “I used to love to cook... I don’t have the strength to stand over a stove, or a barbecue, or anything to, for a long period of time to cook a meal.” Other physical impacts of aBCC that were discussed less commonly included needing to rest more often ($n = 10$; 67%), difficulties doing strenuous activities ($n = 9$; 60%), needing help with day-to-day activities ($n = 8$; 53%), trouble sleeping ($n = 8$; 53%), work limitations ($n = 4$; 27%), and difficulties walking ($n = 3$; 20%).

Social impacts of aBCC were discussed less commonly than physical or emotional/psychological impacts. Challenges with social interactions and modifications to activities to avoid the sun were described by eight (53%) and seven (47%) participants, respectively.

Most Bothersome Patient-Reported Symptoms and Impacts

As part of the interview guide, participants were also asked to identify the top three symptoms and/or impacts associated with their aBCC condition which were considered to be the most bothersome (Table 4). Most participants tended to pick impacts rather than symptoms as their most bothersome concept, consistent with the finding that participants were more likely to discuss impacts than symptoms during the interviews. In total across all categories, the most commonly selected symptom was fatigue and tiredness ($n = 7$) and the most commonly selected impact was the emotional impact of anxiety, worry, and fear ($n = 6$). Some participants selected overarching rather than specific concepts as the most bothersome, such as the inability to “live a normal life” because of their aBCC ($n = 3$).

DISCUSSION

Most patients with aBCC discontinue the currently recommended first-line treatment comprising HHIs (vismodegib or sonidegib) because of adverse events or disease progression [5, 13, 14]. To our knowledge, there is limited literature examining the experiences of patients living with aBCC post HHI treatment. Through

in-depth interviews and qualitative thematic analysis, we were able to determine the reported symptoms and impacts most important to this patient population. We developed a conceptual model and identified whether concepts important to patients with aBCC were captured by widely used instruments that measure HRQoL: the EORTC QLQ-C30 and Skindex-16 questionnaires.

Qualitative interviews with patients who have aBCC and prior HHI treatment identified that the condition has a substantial impact on daily life. The reported impacts of aBCC were discussed more commonly than the reported symptoms, with the most commonly discussed impacts related to emotions and physical function. The reported impacts of aBCC could consistently be mapped back to two concepts: anxiety, worry, and fear, and fatigue and tiredness, consistent with these domains being listed most commonly as bothersome (Table 3). That there were no differences in the data between any of the compared subgroups (sex, race, ethnicity, or clinical status) indicates the concepts are likely to apply to a full range of patients with aBCC.

To our knowledge, the only other qualitative interview study assessing the experience of patients with BCC was conducted by Steenrod et al. [19]. Steenrod et al. and our study identified a number of reported symptoms and impacts in common such as fatigue, itch, pain, impacts on daily activities, and depression. The Steenrod et al. study interviewed patients with nonadvanced and advanced disease in separate cohorts and established that patients with advanced disease experienced a greater impact on their emotional well-being and daily functioning than patients with nonadvanced disease. Unlike in the Steenrod et al. study, participants in our study were mostly female and, per eligibility criteria, all had previously received HHI therapy for aBCC. Owing to differences in the baseline characteristics of the patient populations, comparisons across these studies must be made with caution, but both studies generally portray a significant burden to patients with aBCC.

Steenrod et al. recommended that while HRQoL domains should evaluate changes in

Table 4 Most bothersome patient-reported symptoms and impacts

Concept	Sub-concept	Number of times concepts selected as		
		First most bothersome concept	Second most bothersome concept	Third most bothersome concept
Symptoms	Fatigue and tiredness	3	3	1
	Itch	–	3	1
	Physical appearance (scarring, open wounds, etc.)	1	1	2
	Pain	–	–	1
	Lack of physical strength	2	–	–
	Diarrhea	–	1	–
Physical impacts	Limitations with hobbies or leisure activities	–	1	–
	Difficulties doing strenuous activities	–	1	–
Emotional/psychological impacts	Anxiety, worry, fear	2	3	1
	Low mood or depression	1	–	–
	Frustration, anger, irritability	–	–	1
	Embarrassment	1	–	–
Social impacts	Challenges with social interactions	2	–	2
Other responses	Living normal life	3	–	–
No response/refused to answer		–	2	6

daily activities among patients with nonadvanced disease, a broader assessment that captures changes in lifestyle is needed for patients suffering from advanced disease [19]. The results of our study have made it possible to begin addressing this need by identifying impacts in greater detail than has been done previously. The granularity of results reported in our study allowed for the development of a conceptual model that reflected the patient experience living with aBCC (Fig. 1). Although these concepts have variously been reported previously either in PRO measures or patient interviews, the conceptual model is a new addition that captures them in one place. Of

note, the conceptual model is a visual representation of concepts important to patients, but not necessarily indicative of any theoretical underpinnings.

Consistent with previous findings, patients significantly changed their behavior to mitigate the reported impact of BCC symptoms [19]. For example, patients reported avoiding the sun, covering up, using sunblock, or staying indoors, which was burdensome and impacted their HRQoL. Such behavioral modifications were closely linked with the impact on social interaction, limitation on hobbies and activities, needing help with day-to-day activities, and work impediments. Some concepts described as

“mild” or “not important” still had the potential to substantially impact patients, for example, pain, which although mild in intensity was nonetheless annoying and frustrating.

Recognition is growing for the need to include PRO measures in the clinical investigations of aBCC [35]. PRO measures such as the EORTC QLQ-C30 [20] and Skindex-16 [21], which are commonly used in clinical trials for aBCC, provide a list of symptoms and impacts which patients score to assess their quality of life. As a descriptive exercise, we mapped participant responses and the resulting conceptual model to these PRO questionnaires to examine where concept coverage exists or may require adjustment. Results from the current study validated the use of EORTC QLQ-C30 and Skindex-16 questionnaires for aBCC, but also provided patients the opportunity to identify new concepts that may not have been covered by these PROs. Skin cancer perception by others and modifications to activities to avoid the sun were not explicitly captured by these instruments, although sun avoidance was likely considered by patients while answering EORTC QLQ-C30 Item 7 (hobbies or leisure activities) and Skindex-16 Item 16 (work or do what you enjoy). Overall, most of the core concepts identified during the qualitative interviews were appropriately captured between both the EORTC QLQ-C30 and the Skindex-16, when these two instruments were used together to assess a patient’s HRQoL. The Skin Cancer Index, a PRO instrument recently developed based on expert opinion, patient feedback, and existing literature [36], may also be useful to include in future investigations of patients’ experience living with aBCC. To date it has seen limited use in clinical trials for BCC.

Qualitative research is intentionally based on a small sample size with an emphasis on in-depth analysis of the patient experience. Therefore, no statistical testing was conducted as part of this study. Because saturation depends on homogeneity of the sample and the concepts under study, and since saturation was achieved at 15 patients, it is likely that the issues discussed were relevant to this patient group and

that no pertinent issues were overlooked. However, one limitation to this study is that it was only conducted in the USA and may not represent a sufficiently heterogeneous population to reflect patients with aBCC worldwide. Also, recruiters were unable to meet the study quota for seven patients with aBCC who had progressed at 6 months post HHI cessation; only two (13%) were recruited for this quota. These patients may have a different experience of their disease and may be underrepresented in the study, although the time in months since HHI therapy discontinuation varied widely among the participants, with a median (range) of 2.8 (0.7–9.1) months (Table 2). Additionally, the reason for initial discontinuation of HHI therapy is unknown (e.g., tolerability, disease progression, etc.). Depending on the specific reason(s) for discontinuing HHIs, patients may have different lived experience with their aBCC. Face-to-face interviews would have enabled the interviewers to ascertain non-verbal cues in addition to verbal responses. Whilst observing these non-verbal cues may have further enhanced communication and discussions, our focus was on themes emerging from what was spontaneously said and thus empirically driven. In this respect, the change in mode of data collection is unlikely to have impacted the results.

CONCLUSIONS

This qualitative study highlights the substantial burden aBCC imposes on the daily lives of patients following first-line systemic therapy with HHIs. Patient-reported symptoms and impacts identified as most bothersome were fatigue and tiredness, anxiety, worry, and fear. A common theme expressed by patients was the inability to lead a normal life. Given that patients with aBCC often discontinue first-line systemic therapy with HHIs because of disease progression or intolerance, there is an unmet need for second-line therapies to address the needs of patients and improve their HRQoL.

ACKNOWLEDGEMENTS

The authors thank the participants involved in this study and the collaborating physicians who helped recruit them.

Funding. This study was funded by Regeneron Pharmaceuticals, Inc., and Sanofi. The Rapid Service Fee for publication was also funded by Regeneron Pharmaceuticals, Inc., and Sanofi.

Medical Writing, Editorial, and Other Assistance. Medical writing and editorial support under the direction of the authors were provided by Daniel M. Himmel, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc., and Sanofi according to Good Publication Practice guidelines (<https://www.acpjournals.org/doi/10.7326/M15-0288>). Responsibility for all opinions, conclusions, and data interpretation lies with the authors. All authors reviewed the results from the analyses and supported the interpretation.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Conceptualization: Gerasimos Konidaris, Diana Rofail, Jason Randall, Patrick R. LaFontaine, Chieh-I Chen, Denise Bury, Medha Sasane, Tara Symonds; Data acquisition: Jason Randall, Ashley Geiger, Tara Symonds; Data analysis and interpretation: All authors; Critical review: All authors; Writing and editorial support: Prime, Knutsford, UK.

Disclosures. Gerasimos Konidaris, Patrick R. LaFontaine, and Medha Sasane are employees of and shareholders in Sanofi. Diana Rofail and Chieh-I Chen are employees of and shareholders in Regeneron Pharmaceuticals, Inc. Jason Randall, and Tara Symonds are employees of Clinical Outcomes Solutions. Ashley Geiger is an employee of IQVIA. Denise Bury is a

shareholder in Sanofi, a previous employee of Sanofi, and current employee of Novartis AG.

Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Before recruiting patients, all study documents were submitted to and deemed exempt by the Western Institutional Review Board[®], submission number 2613817-44521595. Exemption status was granted based on the low-risk nature of the study, and due to minimal personal health information being collected. All patients provided informed consent to participate in the study.

Data Availability. The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Mohan SV, Chang AL. Advanced basal cell carcinoma: epidemiology and therapeutic innovations. *Curr Dermatol Rep.* 2014;3:40–5. <https://doi.org/10.1007/s13671-014-0069-y>.

2. Urban K, Mehrmal S, Uppal P, Geisey RL, Delost GR. The global burden of skin cancer: a longitudinal analysis from the Global Burden of Disease Study, 1990–2017. *J Am Acad Dermatol Int.* 2021;2: P98–108. <https://doi.org/10.1016/j.jdin.2020.10.013>.
3. Trakatelli M, Morton C, Nagore E, et al. Update of the European guidelines for basal cell carcinoma management. *Eur J Dermatol.* 2014;24:312–29.
4. Monroe M, Kakarala K. Management of advanced basal cell carcinoma of the head and neck. *Otolaryngol Clin North Am.* 2021;54:271–80. <https://doi.org/10.1016/j.otc.2020.11.003>.
5. Niebel D, Sirokay J, Hoffmann F, et al. Clinical management of locally advanced basal-cell carcinomas and future therapeutic directions. *Dermatol Ther (Heidelb).* 2020;10:835–46. <https://doi.org/10.1007/s13555-020-00382-y>.
6. Goldenberg G, Karagiannis T, Palmer JB, et al. Incidence and prevalence of basal cell carcinoma (BCC) and locally advanced BCC (LABCC) in a large commercially insured population in the United States: a retrospective cohort study. *J Am Acad Dermatol.* 2016;75:957–66. <https://doi.org/10.1016/j.jaad.2016.06.020>. (e2).
7. Migden MR, Chang ALS, Dirix L, Stratigos AJ, Lear JT. Emerging trends in the treatment of advanced basal cell carcinoma. *Cancer Treat Rev.* 2018;64: 1–10. <https://doi.org/10.1016/j.ctrv.2017.12.009>.
8. Sun Pharma Global FZE. Summary of product characteristics: Odomzo 200 mg hard capsules (sonidegib). 2020. https://www.ema.europa.eu/en/documents/product-information/odomzo-epar-product-information_en.pdf. Accessed Jun 10 2021.
9. Sun Pharma Global FZE. Highlights of prescribing information: Odomzo® (sonidegib) capsules, for oral use. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205266s004lbl.pdf. Accessed Jun 10 2021.
10. Roche. Highlights of prescribing information: Eri-vedge (vismodegib) capsules, for oral use. 2020. https://www.gene.com/download/pdf/erivedge_prescribing.pdf. Accessed Jun 10 2021.
11. Roche. Summary of product characteristics: Eri-vedge 150 mg hard capsules (vismodegib). 2016. https://www.ema.europa.eu/en/documents/product-information/erivedge-epar-product-information_en.pdf. Accessed Jun 10 2021.
12. Migden MR. Targeted therapies in the treatment of advanced basal cell carcinoma. *Clin Res Trials.* 2018;4:1–6. <https://doi.org/10.15761/CRT.1000231>.
13. Sekulic A, Migden MR, Basset-Seguín N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer.* 2017;17:332. <https://doi.org/10.1186/s12885-017-3286-5>.
14. Stratigos A, Sekulic A, Peris K, et al., editors. LBA47: Primary analysis of phase 2 results for cemiplimab in patients with locally advanced basal cell carcinoma (laBCC) who progress on or are intolerant to hedgehog inhibitors (HHIs). Poster presented at European Society of Medical Oncology (ESMO) Virtual Congress, September 19–21; 2020.
15. Regeneron Pharmaceuticals IaS-AUL. LIBTAYO®[cemiplimab-rwlc] injection full US prescribing information; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf. Accessed Oct 17, 2022
16. Shingler SL, Garside J, Samanta K, et al. Utilities for advanced basal cell carcinoma. *J Med Econ.* 2013;16:777–83. <https://doi.org/10.3111/13696998.2013.800822>.
17. Mathias SD, Chren MM, Colwell HH, et al. 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.* 2014;150:169–76. <https://doi.org/10.1001/jamadermatol.2013.5870>.
18. Mathias SD, Chren MM, Crosby RD, et al. Reliability and validity of the Advanced Basal Cell Carcinoma Index (aBCCdex). *Br J Dermatol.* 2015;173:713–9. <https://doi.org/10.1111/bjd.13877>.
19. Steenrod AW, Smyth EN, Bush EN, et al. A qualitative comparison of symptoms and impact of varying stages of basal cell carcinoma. *Dermatol Ther (Heidelb).* 2015;5:183–99. <https://doi.org/10.1007/s13555-015-0081-6>.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. 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.* 1993;85:365–76. <https://doi.org/10.1093/jnci/85.5.365>.
21. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. *Dermatol Clin.* 2012;30:231–6. <https://doi.org/10.1016/j.det.2011.11.003>. (xiii).
22. Chernyshov PV, Lallas A, Tomas-Aragones L, et al. Quality of life measurement in skin cancer patients: literature review and position paper of the European Academy of Dermatology and Venereology Task Forces on Quality of Life and Patient Oriented

- Outcomes, Melanoma and Non-Melanoma Skin Cancer. *J Eur Acad Dermatol Venereol.* 2019;33:816–27. <https://doi.org/10.1111/jdv.15487>.
23. Stratigos AJ, Chen C-I, Ivanescu C, et al. Health-related quality of life (HRQoL) in patients (pts) with locally advanced basal cell carcinoma (laBCC) treated with cemiplimab: analysis of a phase II, open-label clinical trial. *Future Oncol.* 2022. https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.9566.
 24. Hansson J, Bartley K, Karagiannis T, et al. Assessment of quality of life using Skindex-16 in patients with advanced basal cell carcinoma treated with vismodegib in the STEVIE study. *Eur J Dermatol.* 2018;28:775–83. <https://doi.org/10.1684/ejd.2018.3448>.
 25. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310:2191–4.
 26. Soleymani AD, Scheinfeld N, Vasil K, Bechtel MA. Metastatic basal cell carcinoma presenting with unilateral upper extremity edema and lymphatic spread. *J Am Acad Dermatol.* 2008;59:S1–3. <https://doi.org/10.1016/j.jaad.2007.08.041>.
 27. Danial C, Lingala B, Balise R, et al. Markedly improved overall survival in 10 consecutive metastatic basal cell carcinoma patients. *B J Dermatol.* 2013;169:673–6.
 28. Moser S, Borm J, Mihic-Probst D, Jacobsen C, Gujer AK. Metastatic basal cell carcinoma: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2014;117:e79-82.
 29. Willig C. *Introducing qualitative research in psychology.* Berkshire: Open University Press; 2013.
 30. QSR International Pty Ltd. NVivo 10. 2014.
 31. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Res Psychol.* 2006;3:77–101.
 32. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods.* 2006;18:59–82.
 33. Bowling A. *Research methods in health: investigating health and health services.* 3rd ed. Maidenhead: Open University Press; 2009.
 34. Bryman A, Burgess B. *Analyzing qualitative data.* New York: Routledge; 2002.
 35. Schlessinger DI, Reynolds KA, Dirr MA, et al. Development of a core outcome set for basal cell carcinoma (BCC). *J Am Acad Dermatol.* 2022;87:573–81. <https://doi.org/10.1016/j.jaad.2022.04.059>.
 36. Lee EH, Klassen AF, Nehal KS, et al. A systematic review of patient-reported outcome instruments of nonmelanoma skin cancer in the dermatologic population. *J Am Acad Dermatol.* 2013;69:e59-67. <https://doi.org/10.1016/j.jaad.2012.09.017>.