Clinical Characteristics of an Italian Patient Population with Advanced BCC and Real-Life Evaluation of Hedgehog Pathway Inhibitor Safety and Effectiveness

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Keywords
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Abstract
Background: Advanced basal cell carcinoma (aBCC) represents a complex and clinically heterogeneous group of lesions for which curative surgery and/or radiotherapy is

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unlikely. Systemic therapy with hedgehog pathway inhibitors (HHIs) changed the treatment landscape for this complex patient population. ***Objectives:*** The aims of the present study are to describe the clinical characteristics of a real-life Italian cohort diagnosed with aBCC and to investigate effectiveness and safety of HHI. ***Methods:*** A multicenter observational study was performed by twelve Italian centers in the period January 1, 2016 – October 15, 2022. Patients aged ≥18 years and diagnosed with aBCC (locally advanced [laBCC] and metastatic BCC [mBCC]) were eligible for the study. Methods for investigating tumor response to HHI included clinical and dermatoscopic evaluation, radiological imaging, and histopathology. For HHI safety assessment, therapy-related adverse events (AEs) were reported and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. ***Results:*** We enrolled 178 patients under treatment with HHI: 126 (70.8%) and 52 patients (29.2%) received sonidegib and vismodegib, respectively. Comprehensive data on HHI effectiveness and disease outcome were available for 132 (74.1%) of 178 patients: 129 patients had a diagnosis of laBCC (n = 84, sonidegib; n = 45, vismodegib) and 3 patients of mBCC (n = 2, vismodegib; n = 1, sonidegib, off-label). Objective response rate was 76.7% (95% confidence interval [CI]: 82.3–68.7) and 33.3% (95% CI: 88.2–1.7) for laBCC (complete response [CR]: 43/129; PR: 56/129) and mBCC (CR: 0/3; PR: 1/3), respectively. High-risk aBCC histopathological subtypes and occurrence of >2 therapy-related AEs were significantly associated with nonresponse to HHI therapy ([OR: 2.61; 95% CI: 1.09–6.05; p: 0.03] and [OR: 2.74; 95% CI: 1.03–7.9; p: 0.04]), respectively. Majority of our cohort (54.5%) developed at least 1 therapy-related AE, most of which were mild-moderate in severity. ***Conclusions:*** Our results demonstrate the effectiveness and safety profile of HHI and confirm the reproducibility of pivotal trial results in real-life clinical setting.

Introduction

Basal cell carcinoma (BCC) is the most common malignancy in white individuals, and it accounts for about 75% of all skin cancers [1]. Majority of BCCs are diagnosed in an early, easy-to-treat stage, and are successfully managed with surgery and/or radiation therapy [2].

Advanced BCC (aBCC) accounts for less than 1% of all BCC diagnoses, and it includes locally advanced BCC (laBCC) and metastatic BCC (mBCC), for which surgery and/or radiation therapy is unlikely to be curative due to tumor and/or patient-related factors [2]. LaBCCs represent a complex and clinically heterogeneous group of lesions characterized by (i) extensive tissue destruction and local tumor infiltration; (ii) multiple treatment failures and tumor relapses; (iii) unacceptable rate of patients' complications resulting from therapeutic interventions [3]. MBCCs are very rare, and they present with lymph nodes and/or internal organs involvement [2].

Systemic therapy with hedgehog pathway inhibitors (HHIs) represents the standard of care for aBCC patients [4]. Vismodegib was the first selective smoothened (SMO) inhibitor, and it is approved in the USA, European Union, Switzerland, and Australia for adult patients with mBCC and laBCC who are not candidates for surgery and radiotherapy [5]. Sonidegib is also a SMO inhibitor, with similar clinical indications in Switzerland and Australia; its use is restricted to laBCCs in the other countries [6].

Patients' profile, tumor characteristics, and response to therapy need to be better characterized in real-world clinical scenarios, to provide evidence on HHI safety and effectiveness. The aims of the present study are (1) to describe clinical features and disease characteristics of an Italian cohort diagnosed with aBCC under treatment with HHI and (2) to assess real-life effectiveness and safety of HHI therapy.

Patients and Methods

Study Design and Data Collection

A multicenter observational study was conducted in twelve Italian Dermatological centers, in the period from January 1, 2016, to October 15, 2022. Patients aged ≥18 years and diagnosed with a histologically confirmed aBCC (laBCC and mBCC) who attended, either upon first visit or on follow-up, the outpatient clinics of the involved centers were eligible for the study. Patients who were already on HHI treatment before January 2016 could also be included in the study. The study protocol was approved by the Local Ethical Committees of each center.

LaBCCs included tumors which could not be cured or were unlikely to be cured by surgery and/or radiation therapy as per decision of the local multidisciplinary tumor board. Investigators were asked to further specify among the following: unsatisfactory esthetic outcome after surgery and/or radiotherapy, expected mutilation after surgery, ill-defined tumor margins, aggressive histopathological subtype, multiple recurrences, presence of multiple BCCs on the same anatomical area, previous radiotherapy, patient's age and comorbidities which made surgery impossible, patient's refusal to undergo surgery and/or radiotherapy. mBCCs included lymph nodes and/or visceral organ BCC metastases.

Data were collected via a semi-anonymous questionnaire which patients answered at the outpatient clinics. The following information was registered: (i) patients' demographic data (age, sex,

Table 1. Patients' clinical characteristics

Baseline patients' characteristics (*N* = 178)	*N* (%)
Age, mean (standard deviation)	72.3 (13.9)
Sex	
Male	114 (64)
Female	64 (36)
Cardiovascular comorbidities	
Yes	109 (61.2)
No	69 (38.8)
Internal malignancy	
Yes	25 (14)
No	153 (86)
OTR	
Yes	2 (1.1)
No	176 (98.9)
ECOG PS	
0	99 (55.6)
1	55 (31)
2	20 (11.2)
3	4 (2.2)
4	0 (0)
Gorlin syndrome	
Yes	19 (10.7)
No	159 (89.3)
Fitzpatrick skin type	
Type 1	30 (16.9)
Type 2	75 (42.1)
Type 3	73 (41)
Type 4	0 (0)
Solar lentigines	
Yes	101 (56.8)
No	77 (43.2)
Actinic keratosis	
Yes	84 (47.2)
No	94 (52.8)
Previous BCC (other than target BCC)	
Yes	78 (43.8)
No	100 (56.2)
Concomitant BCC (other than target BCC)	
Yes	87 (48.9)
No	91 (51.1)
BCC condition	
laBCC	172 (96.8)
mBCC	6 (3.2)
Metastatic sites	
Lymph nodes	4 (58.4)
Bone	2 (16.7)
Lung	1 (8.3)
Liver	1 (8.3)
Skin	1 (8.3)
BCC anatomical site	
Head and neck	138 (77.5)
Trunk	19 (10.7)
Limbs	15 (8.4)
Other	6 (3.4)
Histopathological subtype	
Superficial	35 (19.7)
Nodular	51 (28.6)
Infiltrative	62 (34.8)
Morpheaform	8 (4.5)
Basosquamous	12 (6.8)
Adenoid-cystic	7 (3.9)
Micronodular	2 (1.1)
Sarcomatoid differentiation	1 (0.6)

BCC, basal cell carcinoma; ECOG PS, eastern cooperative oncology group performance status; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; *N*, number; OTR, organ transplant recipients.

ethnicity, level of education, occupational status, comorbidities), patients' phenotype (hair color at the age of 18, eye color), patients' habits (occupational and/or recreational sun exposure, use of photoprotection, use of phototherapy, smoking); dermatologists assessed the following characteristics: (ii) patients' clinical examination (skin type according to Fitzpatrick classification, eastern cooperative oncology group performance status [ECOG PS], presence of solar lentigines and actinic keratoses, previous diagnosis of BCCs, squamous cell carcinoma [SCC], and melanoma, concomitant diagnosis of BCCs, squamous cell carcinomas, and melanoma); (iii) aBCC characteristics (anatomical area, histopathological subtype, lymph nodes and/or visceral organ metastases, previous treatments, systemic treatment with HHI, best tumor response to HHI, intermittent HHI schedule) and patients' vital status.

Effectiveness and Safety Variables

Assessment of tumor response to HHI was performed by dermatologists at each of the twelve centers, and methods included: clinical and dermatoscopic evaluation of the aBCC lesions, radiological imaging, and tumor response classification as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and histopathology. Complete response (CR) was defined as absence of clinical and dermatoscopic signs related to the BCC lesion, disappearance of the target lesion on radiologic imaging, or absence of residual BCC on histopathology; partial response (PR) included ≥30% reduction of clinically visible or radiologic sum of the longest diameter of the target lesion compared to baseline; progressive disease (PD) was defined as ≥20% increase of externally visible or radiologic sum of the longest diameter of the target lesion or appearance of new lesions compared to baseline; stable disease (SD) encompassed patients who did not meet PR or PD criteria. Treatment effectiveness outcomes were objective response rate (ORR), defined as the proportion of patients achieving CR or PR at any time during follow-up, and disease control rate (DCR), including patients who reached CR, PR, or SD at any time during follow-up. Treatment duration of sonidegib and vismodegib was calculated as the time from the first dose of the drug to treatment discontinuation due to any reasons. Patients who were alive or

continued treatment beyond our data cut-off (October 15, 2022) were censored at the date of the last follow-up visit. For HHI safety assessment, dermatologists recorded the occurrence of therapy-related adverse events (AEs) and graded them according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Continuous variables were reported as mean and standard deviation for normally distributed data or median and range if distribution was skewed. Categorical variables were summarized as numbers and percentages. Univariable and multivariable logistic regressions were used to investigate the association between tumor response (CR + PR vs. SD + PD) and patients' clinical characteristics; results were presented as odds ratio (OR) with 95% confidence interval (CI). A p value <0.05 was chosen as a threshold level of statistical significance. All statistical analyses were performed with GraphPad Prism, version 9.0.

Results

Patients and Tumors' Characteristics

Overall, 178 aBCC patients were recruited in the study, as shown in Table 1. Majority of patients were men (n = 114, 64%), and mean age at the time of diagnosis of the aBCC was 72.3 years (standard deviation: 13.9). More than half of patients reported cardiovascular comorbidities (n = 109, 61.2%), 25 patients (14%) had a personal history of internal malignancy, and 2 patients (1.1%) were organ transplant recipients. ECOG PS was 0–1 in 154/178 (86.6%) patients. Nineteen patients (10.7%) had Gorlin syndrome.

LaBCCs and mBCCs accounted for 96.6% (n = 172) and 3.4% (n = 6) of all aBCC diagnoses (shown in Table 1). Metastatic sites included lymph nodes (n = 4), bone (n = 2), liver (n = 1), lung (n = 1), and skin (n = 1). The most common laBCC characteristics were ill-defined tumor margins (n = 93, 42.3%), multiple recurrences (n = 68, 30.9%), and expected mutilation after surgery (n = 66, 30%). Infiltrative BCC was the most frequent histopathologic subtype (n = 62, 34.8%); the other histopathologic variants were as follows: nodular type (n = 51, 28.6%), superficial type (n = 35, 19.7%), basosquamous (n = 12, 6.8%), morpheaform (n = 8, 4.5%), adenoid-cystic with metatypical aspects (n = 7, 3.9%), micronodular (n = 2, 1.1%), and BCC with sarcomatoid differentiation (n = 1, 0.6%). Majority of the laBCCs were located on the head and neck area (n = 138, 77.5%), with 24/138 (17.4%), 24/138 (17.4%), and 27/138 (19.6%) arising on the scalp, temples, and nose, respectively.

Concerning patients' clinical examination (shown in Table 1), Fitzpatrick skin type I, II, and III were observed in 30, 75, and 73 patients, respectively. Previous and concomitant diagnosis of BCCs, other than the target aBCC lesions, involved 78/178 (43.8%) and 87/178 (48.9%) patients, respectively, with a mean number of concomitant nontarget BCCs of 3 (standard deviation: 7.9).

HHI Effectiveness and Disease Outcome

Comprehensive data on HHI effectiveness were available for 132 (74.1%) of 178 patients (shown in Table 2): 129 patients had a diagnosis of laBCC (n = 84, sonidegib; n = 45, vismodegib), and 3 patients of mBCC (n = 2, vismodegib; n = 1, sonidegib, off-label). The sonidegib and vismodegib cohorts differed for some clinical and histopathological variables (high-risk BCC histopathological subtypes [p: 0.003], and occurrence of >2 AEs [p: 0.01] were more frequent in the vismodegib subgroup); mean age, sex, ECOG PS, and site of occurrence BCC were homogeneously distributed among the two cohorts. ORR was 76.7% (95% CI: 82.3–68.7) and 33.3% (95% CI: 88.2–1.7) for laBCC (CR: 43/129; PR: 56/129) and mBCC (CR: 0/3; PR: 1/3), respectively. DCR was 95.3% (95% CI: 97.9–90.2) for laBCC patients and 66.7% (95% CI: 98.3–11.8) for mBCC.

Vismodegib

Forty-seven of 132 patients underwent treatment with vismodegib (n = 45 laBCC; n = 2 mBCC), shown in Table 2. Median treatment duration was 17 months (range: 1–111), and median time to treatment response was 8 months for (range: 1–42). For laBCC, ORR was 66.7% (95% CI: 78.6–52.1), with 7/45 CR and 23/45 PR; DCR was as follows: 91.1% (95% CI: 96.5–79.3). For mBCC, we assessed 1 patient with SD and 1 with PD.

Sonidegib

Eighty-five of 132 patients received sonidegib treatment (n = 84 laBCC; n = 1 mBCC), shown in Table 2. Median treatment duration was 6 months (range: 1–66), and median time to treatment response was 6 months (range: 1–30). For laBCC, ORR, and DCR were 82.1% (95% CI: 88.9–72.6) and 97.6% (95% CI: 99.6–91.7), respectively; we reported 1 PR in a mBCC patient.

Clinical and Histopathological Predictors of Response to HHI

We investigated whether an association existed between clinical and histopathological characteristics of our cohort and response to HHI (CR + PR vs. SD + PD), as shown in Table 3. High-risk BCC histopathological subtypes were significantly associated with non-response to HHI therapy (OR: 2.61; 95% CI: 1.09–6.05; p: 0.03). Similarly, patients

Table 2. Effectiveness outcomes of HHI therapy

Best response *N* (%)	All patients (*N* = 132)	laBCC (*N* = 129)	mBCC (*N* = 3)	Vismodegib (*N* = 47)		Sonidegib (*N* = 85)	
				laBCC (*N* = 45)	mBCC (*N* = 2)	laBCC (*N* = 84)	mBCC (*N* = 1)
CR	43 (32.6)	43 (33.3)	0 (0)	7 (15.5)	0 (0)	36 (42.8)	0 (0)
PR	57 (43.2)	56 (43.4)	1 (33.3)	23 (51.1)	0 (0)	34 (40.5)	1 (100)
SD	25 (18.9)	24 (18.6)	1 (33.3)	12 (26.6)	1 (50.0)	13 (15.5)	0 (0)
PD	7 (5.3)	6 (4.7)	1 (33.3)	5 (11.1)	1 (50.0)	2 (2.4)	0 (0)
ORR (95% CI)	75.8 (82.3–67.8)	76.7 (83.2–68.7)	33.3 (88.2–1.7)	66.7 (78.6–52.1)	0.0 (82.2–0.0)	82.1 (88.9–72.6)	100 (100–5.1)
DCR (95% CI)	94.7 (97.4–89.5)	95.3 (97.9–90.2)	66.7 (98.3–11.8)	91.1 (96.5–79.3)	50 (97.4–2.6)	97.6 (99.6–91.7)	100 (100–5.1)

CI, confidence interval; CR, complete response; DCR, disease control rate; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; *N*, number; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Association of patients' clinical and histopathological characteristics and disease outcomes with HHI

Variable	Outcome: SD + PD		*p* value
	OR	95% CI	
Age	1.01	0.98–1.04	0.36
Sex			
Male	0.62	0.26–1.49	0.28
Female			
ECOG PS			
0	0.75	0.30–1.78	0.62
1–4			
Anatomical site			
Head and neck	1.81	0.71-4-46	0.18
Other			
Histopathological subtype			
Low risk	2.61	1.09–6.05	***0.03***
High risk*			
Prior therapies			
No	1.76	0.75–4.19	0.21
Yes			
Number of prior surgeries			
0–1	2	0.69–5.9	0.2
≥2			
Occurrence of AEs			
No	1.47	0.62–3.54	0.5
Yes			
Number of AEs			
≤2	2.74	1.03–7.9	***0.04***
>2			

AEs, adverse events; CI, confidence interval; ECOG PS, eastern cooperative oncology group performance status; OR, odds ratio; PD, progressive disease; SD, stable disease. *High-risk histopathological subtypes: infiltrative, morpheaform, micronodular, basosquamous, BCC with sarcomatoid differentiation.

developing >2 therapy-related AEs had nearly a 3-fold increased probability of achieving nonresponse to HHI (OR: 2.74; 95% CI: 1.03–7.9; *p*: 0.04); conversely, we reported a nonsignificant association between occurrence of at least one AE and therapeutic response (*p*: 0.5). At multivariable analysis, none of our predictors was significantly associated with treatment response.

HHI and Safety Outcomes

Collectively, we recorded 309 therapy-related AEs in 97 patients (54.5%), as shown in Table 4. Most patients (*n* = 71, 73.2%) developed ≥2 AEs, and 26 patients (26.8%) experienced one AE only. Muscle spasms were the most common AE (*n* = 86, 27.9%), followed by ageusia and/or dysgeusia (*n* = 82, 26.2%), and alopecia (*n* = 45, 14.6%). Toxicities were mostly mild to moderate in severity, with CTCAE grade 1 and 2 AEs accounting for 50% (*n* = 156) and 30.2% (*n* = 93) of the total, respectively. Serious AEs (CTCAE grade 3–4) affected 32 patients (32.9%), and the most common high-grade toxicities were muscle spasms (*n* = 17) and alopecia (*n* = 12). Age was not significantly associated with occurrence of AEs (OR: 1.02; 95% CI: 0.99–1.04), *p*: 0.12.

Discussion

In the present observational real-life study, we described the clinical characteristics of an Italian cohort diagnosed with aBCC and investigated the effectiveness and safety profile of HHI therapy. Advanced BCC encompasses a complex and clinically heterogeneous group

Table 4. Safety outcomes of HHI therapy

	AEs (*N* = 309), *N* (%)	Sonidegib (*N* = 168), *N* (%)	Vismodegib (*N* = 141), *N* (%)
CTCAE grade 1–2	249 (80.6)	139 (82.7)	110 (78)
CTCAE grade 3–5	60 (19.4)	29 (17.3)	31 (22)
Muscle spasms	86 (27.9)	51 (30.3)	35 (24.8)
Dysgeusia/ageusia	82 (26.2)	45 (26.7)	37 (26.3)
Alopecia	45 (14.6)	19 (11.3)	26 (18.4)
Weakness	37 (12)	21 (12.5)	16 (11.4)
Nausea/vomit	12 (3.9)	6 (3.6)	6 (4.3)
Anorexia	12 (3.9)	0 (0)	12 (8.5)
Weight loss	11 (3.6)	8 (4.8)	3 (2.1)
Diarrhea	7 (2.3)	3 (1.8)	4 (2.8)
Increase in CPK enzyme	6 (1.9)	5 (3)	1 (0.7)
Other	11 (3.6)	10 (6)	1 (0.7)

AEs, adverse events; CPK, creatinine phosphokinase; CTCAE, common terminology criteria for adverse events; *N*, number.

of lesions that typically affect elderly individuals with a male predominance and with increased susceptibility to ultraviolet radiation exposure [2]. In our study, the mean age at diagnosis of the target BCC lesion was 72.3 years; we also reported a higher proportion of male patients, who most commonly presented with fair pigmentary characteristics and who developed aBCC lesions on chronically sun-exposed areas. Altogether, our findings are in line with previous real-life studies exploring aBCC patients, with comparable data on age, sex, and tumor location [7–9].

In our study, ill-defined tumor margins, expected disfigurement or mutilation after surgery, and multiple recurrences accounted for the most common features of aBCC patients. The frequency of these criteria is comparable to the data presented in the pivotal trials ERIVANCE and BOLT [10, 11]. The broad and heterogeneous definition of aBCC highlights a gap in its classification system, which has been partially filled by the new 5-group classification recently proposed by the European Association for Dermato Oncology (EADO) [12, 13], with the aim of assisting clinicians in the definition of aBCC.

We assessed HHI effectiveness outcomes: for laBCC patients treated with vismodegib, we reported an ORR of 66.7% (7/45 CR and 23/45 PR). This figure is similar to the efficacy outcome presented in the pivotal trial ERIVANCE, where investigator-assessed ORR in the laBCC group was 60.3% (95% CI: 47.2–71.7) at 39-month follow-up [14]. A comparable response rate was observed in the single-arm, multicenter, open-label study STEVIE, with an investigator-assessed ORR of 68.5% (95% CI: 65.7–71.3) in the laBCC group [15]. Our effectiveness outcomes confirm the benefit of HHI therapy in a real-life setting, which is often characterized by more complex and fragile patients compared to the population selected for trials. Our cohort included patients with active neoplasia, several comorbidities, an ECOG PS ranging from 0 to 4, and a mean age at diagnosis of the aBCC of 72.3 years. Conversely, eligibility criteria in the ERIVANCE trial excluded patients with active neoplasia and with ECOG PS >2, and the enrolled patients had a mean age of 61.4 years [10]. In our patient population, median time to vismodegib response was 8 months; this figure is higher compared to the median time reported in the ERIVANCE trial (140 days) [14]. The different composition of our study population including more fragile and elderly patients may account for this discrepancy. Concerning laBCC patients on sonidegib therapy, we assessed an ORR of 82.1% (36/84 CR and 34/84 PR). This figure is similar to a French real-life retrospective study on sonidegib in 21 aBCC patients, where investigators reported an ORR of 81% (95% CI: 59–95) [7]. The pivotal trial BOLT reported an ORR as per central review of 56% (95% CI: 43–68) for laBCC patients in the 200 mg sonidegib group at 42-month follow-up [16]. In the BOLT trial, efficacy outcomes were evaluated based on the modified RECIST criteria, which are particularly stringent especially with regard to CR assessment [17].

We acknowledge that direct comparison of real-life studies and pivotal trials is limited by the assessment methods for tumor response. In routine clinical practice, dermatologists' clinical evaluation represents the most common method for tumor response assessment, compared to imaging and histopathology. This difference in assessment methods may account for the discrepancy in tumor response. Furthermore, in our study, we must acknowledge a significant difference in the cohort

composition between sonidegib and vismodegib subgroups, where high-risk aBCC histopathological subtypes and occurrence of >2 AEs were significantly more represented in the vismodegib cohort. Altogether, these imbalances might explain the different ORR between our sonidegib and vismodegib laBCC subgroups (82.1% vs. 66.7%, respectively), especially with regard to CR (36/84 vs. 7/45, respectively).

We investigated the association between clinical and histopathological characteristics of our cohort and tumor response to HHI: high-risk aBCC histopathological subtypes were significantly associated with a higher probability of nonresponse to therapy. Infiltrative type BCC was the most frequent histopathological subtype, accounting for 34.8% of all aBCC diagnoses. The high prevalence of this histopathological subtype has been reported also in pivotal trials and real-life studies on aBCC [7, 9–11, 18], where a similar association between high-risk histology and decreased tumor response has been described [19]. Occurrence of >2 AEs was also significantly associated with a higher probability of nonresponse to HHI. Patients experiencing multiple AEs might undergo dose reduction or treatment discontinuation, which may affect tumor response outcomes. To this regard, some authors reported an association between intermittent dosing and nonresponse to HHI [18, 20], while others claimed an unchanged efficacy profile [21–23].

Concerning HHI safety profile, 54.5% of patients developed ≥1 HHI-induced AE. This figure is lower compared to the AE frequency reported in the ERIVANCE and BOLT trials, where 100% and 98% of the enrolled patients experience ≥1 toxicity [10, 11]. Clinicians gained significant experience in the management of common AEs, warranting prompt patient referral to nutritionists to avoid weight loss, as well as suggesting exercise to prevent muscle spasms; altogether, this may account for the different AE frequency in our real-life population. Consistently with previous studies, we most commonly assessed mild to moderate AEs, with muscle spasms, dysgeusia, and alopecia being the three most common HHI-induced toxicities [10, 11, 24]. In conclusion, our study describes the clinical features of a real-life Italian cohort diagnosed with aBCC, and it confirms the effectiveness and safety profile of the HHI therapy in a real-world setting.

Key Message

Our study confirms the HHI safety and effectiveness in real-world clinical practice.

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent has been collected from participants in order to participate to the study. This study protocol was reviewed and approved by the Ethical Committee of Catholic University of the Sacred Heart, approval number 3890.

Conflict of Interest Statement

Gabriella Fabbrocini reports payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Abiogen, Almirall, Celgene, Eli Lilly, LeoPharma, Novartis, Sanofi, and UCB. Emi Dika reports consulting fees from SunPharma, Difacooper, and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from SunPharma, Difacooper, and Novartis, La Roche Posay: support for attending meetings and/or travel from SunPharma, Difacooper, and Novartis; participation on data safety monitoring board or advisory board from SunPharma and Novartis; receipt of equipment materials, drugs from SunPharma.

Paolo Antonio Ascierto reports grants or contracts from Bristol Myers Squibb, Roche-Genentech, Pfizer/Array, and Sanofi; consulting fees from Bristol Myers Squibb, Roche-Genentech, Merck Sharp and Dohme, Novartis, Merck Serono, Pierre Fabre, SunPharma, Sanofi, Idera, Sandoz, 4SC, Italfarmaco, Nektar, Pfizer/Array, Lunaphore, Medicenna, Bio-Al Health, ValoTx, Replimmune, and Bayer; support for attending meetings and/or travel from Pfizer, Bio-Al Health, and Replimmune; participation on data safety monitoring board or advisory board from Bristol Myers Squibb, Roche-Genentech, Merck Sharp and Dohme, Novartis, AstraZeneca, Immunocore, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Oncosec, Nouscom, Seagen, and iTeos. Maria Concetta Fargnoli reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from SunPharma; support for attending meetings and/or travels from SunPharma.

Luca Bianchi reports consulting fees from Novartis, Janssen, SunPharma, Pfizer, Biogen, Abbvie, Eli Lilly, Leopharma; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis, Janssen, SunPharma, Pfizer, Biogen, Abbvie, Eli Lilly, Leopharma; participation on data safety monitoring board or advisory board from Novartis, Janssen, SunPharma, Pfizer, Biogen, Abbvie, Eli Lilly, Leopharma. Piergiacomo

Calzavara-Pinton reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Abbvie, Galderma, Almirall, Leo, Cantabria, Novartis, and Bohringer Ingelheim; participation on data safety monitoring board or advisory board from Sanofi, Abbvie, Pfizer, Almirall, Leo, Cantabria, MSD, Bohringer Ingelheim, and Novartis.

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Author Contributions

Writing and revision of the manuscript and interpretation of data: Maria Mannino. Data collection and study supervision: Alfredo Piccerillo, Gabriella Fabbrocini, Pietro Quaglino, Giuseppe Argenziano, Emi Dika, Paolo Antonio Ascierto, Giovanni Pellacani, Caterina Longo, Maria Concetta Fargnoli, Luca Bianchi, Piergiacomo Calzavara-Pinton, Iris Zalaudek, Paolo Fava, Massimiliano Scalvenzi, Enrico Bocchino, Alessandro Di Stefani, and Ketty Peris. Conception and design of the study: Ketty Peris.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author, Ketty Peris.

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