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Original Research

Switch to every-other-day sonidegib dose reduction schedule in advanced basal cell carcinoma: a multicenter retrospective observational study on effectiveness and safety

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ABSTRACT

Background: Sonidegib displays class-specific adverse events (AEs), which impair therapeutic adherence. Every-other-day administration is within the label of sonidegib approval.
Objective: to investigate the effectiveness and safety profile of every-other-day sonidegib in locally advanced basal cell carcinoma (laBCC) patients after a course of once-daily sonidegib.
Methods: a multicenter retrospective observational study was performed at 15 Italian tertiary-referral centers (January 2016 – May 2024). Fisher's exact and Mann-Whitney test detected differences between the cohorts. Kaplan-Meier method estimated progression free survival (PFS). Univariate and multivariate logistic regressions investigated the association with switching to the every-other-day schedule.
Results: 165 laBCC patients were enrolled, of whom 60 switched from once-daily to every-other-day sonidegib. Median sonidegib treatment duration was 14 months (range: 1–26) in the continuous regimen cohort, and 23 months (range: 6–29) in the reduced regimen cohort, p value < 0.0001. The objective response rate (ORR) was 80.8 % (95 % confidence interval [CI]: 87.4–72) and 84.8 % (95 % CI: 91.6–74.3) for patients on the once-daily and on the every-other-day sonidegib schedule, respectively. Median duration of response was 9.5 months

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(range: 1–37) and 6 months (range: 1–28) in the continuous and in the reduced regimen cohorts, respectively. PFS probability was reduced in the every-other-day sonidegib group compared to the once-daily group (hazard ratio: 4.8, 95 % CI: 1.10–21.27; p = 0.003). 62.6 % and 19.7 % patients experienced at least one AE on the once-daily and on the every-other-day schedule, respectively, p value < 0.0001.
Conclusion: Switch to the every-other-day sonidegib schedule is safe and effective, albeit with reduced tumor control in the long-term.

1. Introduction

Basal cell carcinoma (BCC) is the most common cutaneous malignancy, accounting for 75 % of keratinocyte tumors [1]. Incidence rates of BCC are increasing over the last decades, particularly in fair skinned and elderly populations, with an age-standardized incidence rate of a first BCC diagnosis of approximately 304 cases per 100.000 person-years in northern European countries [2–4].

Advanced basal cell carcinoma (aBCC), including locally (la) and metastatic (m) BCC, accounts for less than 1 % of all BCC diagnosis [5]. The term aBCC encompasses a heterogeneous group of lesions for which surgery and radiotherapy are unlikely to be curative [1]. Hedgehog pathway inhibitors (HHI), vismodegib and sonidegib, are Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved as first-line treatment for aBCC patients [1]. Vismodegib 150 mg once-daily is approved for treatment of laBCC and mBCC [6]; sonidegib 200 mg once-daily is approved for laBCC only [7].

Data from the phase II pivotal trials ERIVANCE for vismodegib and BOLT for sonidegib highlighted the occurrence of class-specific adverse events (AEs), among which the most common were muscle spasms, alopecia, dysgeusia, increased creatine phosphokinase (CPK), fatigue and weight loss [8,9]. Despite being usually low-grade in severity, AEs can negatively impact patients' quality of life and adherence to therapy, eventually leading to premature treatment discontinuation and impairment of treatment outcomes [10]. Dose modification schedules and introduction of "drug holidays" are common strategies to maximize patient's adherence to therapy and drug tolerability [11,12]. Sonidegib dose modification schedule to an every-other-day regimen is within the label of the FDA and EMA approval [7]; for vismodegib, up to 8 weeks treatment interruption is allowed in case of intolerable AEs [6]. A few real-life studies investigated the effectiveness and safety profile of the every-other-day sonidegib regimen in aBCC patients, highlighting a gap on whether the dose modification schedule could effectively increase the median duration of treatment, improve tolerability, and maintain effectiveness.

The aim of the present study was to investigate the effectiveness and safety profile of the every-other-day sonidegib regimen in a cohort of laBCC patients who switched to the dose reduction schedule after a course of once-daily sonidegib administration.

2. Patients and methods

2.1. Study design and data collection

We performed a multicenter retrospective observational study at 15 Italian tertiary-referral centers, from January 2016 to May 2024. Inclusion criteria were as follows: adult patients with histologically confirmed diagnosis of laBCC on treatment with sonidegib. Patients were considered eligible for sonidegib treatment as per decision of the multidisciplinary tumor board of each enrolling center. Patients were subsequently divided in two cohorts: the "continuous regimen", including patients on once-daily sonidegib administration, and the "dose reduction regimen", for patients on every-other-day sonidegib dose modification schedule.

Demographic and clinico-pathologic data were collected, such as patient's age and sex, Eastern Cooperative Oncoloogy Group Performance Status (ECOG PS), immunosuppressive status, diagnosis of Gorlin-Goltz syndrome, primary tumor site and histological subtype (superficial and nodular BCCs accounted for the low-risk subtypes; morpheiform, basosquamous, infiltrative, and micronodular BCCs were defined as the high-risk subtypes), treatments prior to HHI, the date of sonidegib start and discontinuation, the date of switch to the dose reduction regimen and the cause for treatment modification, patients' best response along follow-up, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), incidence and severity of AEs. Methods to investigate laBCC response to sonidegib included clinical and dermoscopic examination, and histological assessment. The effectiveness outcome were the objective response rate (ORR), defined as the proportion of patients achieving CR and PR, the duration of response (DOR), defined as the interval from CR and PR assessment until disease progression or death due to any reason, and the progression free survival (PFS), calculated as the time from treatment start until disease progression or death due to any cause. For safety assessment, investigators recorded the occurrence and severity of AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Sonidegib treatment duration was defined as the time from the first dose administration until drug discontinuation due to any reasons. Time to switch to the dose reduction regimen was calculated as the time from the first administration of sonidegib at the once-daily schedule until the dose modification to the every-other-day regimen. Patients who continued treatment beyond our data cutoff were censored at the date of the last follow-up visit.

2.2. Statistical analysis

Categorical variables were reported as number and percentages; continuous variables were summarized as median and range. Fisher's exact test and Mann-Whitney test were used to detect differences between the continuous regimen cohort and the dose reduction regimen cohort for categorical and continuous variables, respectively. The Kaplan-Meier method was used to estimate the PFS probability, and the log-rank test to detect differences between the curves. Univariate and multivariate logistic regressions were used to investigate the variables associated with the probability of switch to the every-other-day sonidegib schedule. Results were presented as odds ratio (OR) with 95 % confidence interval (CI). Besides age and gender, only the variables reaching a statistical threshold of 0.1 at univariate logistic regression were incorporated in the multivariate logistic regression model. A p-value < 0.05 was chosen as threshold level of statistical significance. Statistical analyses were performed with GraphPad Prism, version 10.0.

3. Results

3.1. Patient population

We included 165 laBCC patients on treatment with sonidegib (a subset of these patients has been described already elsewhere [13,14]); demographic and clinico-pathologic features are summarized in Table 1. The median age of our cohort was 79 years (range: 26–99); males accounted for 64.2 % (n = 106), and females represented 35.8 % (n = 59). The ECOG PS was 0–1 in 90.9 % (n = 150) of our population. Sixteen patients (9.7 %) had a diagnosis of Gorlin-Goltz syndrome. LaBCCs were mostly located on the head and neck area (78.8 %, n = 130), and the high-risk histological subtypes accounted for 43 %

Table 1
Demographic and clinico-pathologic features of laBCC patient population.

Variable	Overall cohort N = 165	Continuous regimen N = 99	Dose reduction regimen N = 66	P-value
Age (years), median (range)	79 (26–99)	78 (26–99)	80.5 (28–94)	0.09
Gender, N (%)				
Male	106 (64.2)	61 (61.6)	45 (68.2)	0.4
Female	59 (35.8)	38 (38.4)	21 (31.8)	
ECOG PS, N (%)				
0–1	150 (90.9)	93 (93.9)	57 (86.4)	0.1
2–5	15 (9.1)	6 (6.1)	9 (13.6)	
Immunosuppression, N (%)				
Yes	3 (1.8)	1 (1)	2 (3)	0.5
No	162 (98.2)	98 (99)	64 (97)	
Gorlin-Goltz syndrome, N (%)				
Yes	16 (9.7)	11 (11.1)	5 (7.6)	0.5
No	149 (90.3)	88 (88.9)	61 (92.4)	
LaBCC localization, N (%)				
Head and neck	130 (78.8)	83 (83.8)	47 (71.2)	0.07
Trunk and limbs	35 (21.2)	16 (16.2)	19 (28.8)	
LaBCC histological subtype, N (%)				
High-risk histology*	71 (43)	46 (46.5)	25 (37.9)	0.3
Low-risk histology§	94 (57)	53 (53.5)	41 (62.1)	
Treatments prior to HHI, N (%)				
Yes	97 (58.8)	62 (62.6)	35 (53)	0.2
No	68 (41.2)	37 (37.4)	31 (47)	
Sonidegib duration (months), median (range)	18 (1–29)	14 (1–26)	23 (6–29)	**< 0.0001**

Abbreviations: ECOG PS, eastern cooperative oncology group performance status; HHI, hedgehog pathway inhibitors; LaBCC, locally advanced basal cell carcinoma; N, number.
* high risk histology: morpheiform, basosquamous, infiltrative, and micronodular
§ low risk histology: nodular and superficial

(n = 71) of the diagnoses.

Ninety-nine of the 165 patients (60 %) were on the once-daily sonidegib schedule for the entire treatment duration, accounting for the continuous regimen cohort. The dose reduction regimen cohort was comprised by 66 of the 165 patients (40 %), of whom 60 patients switched to the every-other-day administration after a course of once-daily sonidegib, and 6 patients were on the dose modification schedule from the beginning of therapy due to polypharmacy. The median sonidegib treatment duration was 18 months (range: 1–29) for the overall cohort. Sonidegib treatment duration was significantly longer in the dose reduction regimen cohort, with a median of 23 months (range: 6–29), compared to the continuous regimen cohort (median: 14 months [range: 1–26]), p-value < 0.0001 as shown in Table 1. The median time to dose modification from the once-daily sonidegib administration to the every-other-day schedule was 13 months (range: 1–17). Achievement of CR was the most common cause of switch to the dose reduction schedule (46.6 %, n = 28), followed by occurrence of AEs (38.4 %, n = 23) and development of patients' comorbidities requiring the introduction of medications potentially interfering with sonidegib (15 %, n = 9).

3.2. Effectiveness and safety outcomes

The ORR was 82.4 % (95 % CI: 87.5–75.9) for the overall cohort, with 87/165 (52.7 %) and 49/165 (29.7 %) patients achieving CR and PR, respectively (Table 2). We assessed a comparable ORR in the continuous regimen cohort and in the dose reduction regimen cohort: the ORR was 80.8 % (95 % CI: 87.4–72) for patients on the once-daily sonidegib schedule, and 84.8 % (95 % CI: 91.6–74.3) for patients on the every-other-day sonidegib dose modification schedule. In the continuous regimen group, we reported 46/99 (46.5 %) and 34/99 (34.3 %) CR and PR, respectively; in the dose reduction regimen group, 41/66 (62.1 %) and 15/66 (22.7 %) patients achieved CR and PR, respectively (Table 2). Concerning the 6 patients who were on the every-other-day sonidegib administration from treatment start, 3 achieved PR and 3 achieved SD. DOR was significantly shorter in the dose reduction regimen cohort (median: 6 months [range: 1–28]) compared to the continuous regimen group (median: 9.5 months [range: 1–37]), p value: 0.01 (Table 2). Accordingly, PFS probability was reduced in the every-other-day sonidegib regimen group compared to the once-daily sonidegib group (hazard ratio [HR]: 4.8 (95 % CI: 1.10–21.27) (Fig. 1).

Concerning the safety profile, 108 of 165 (65.5 %) patients developed at least one AE during treatment course. Forty-five of 165 (27.3 %) patients presented with ≥ 3 AEs, most of which were CTCAE grade 1–2 in severity, and 24/165 patients (14.5 %) had at least one AE which was ranked as CTCAE grade ≥ 3. Muscle cramps were the most common toxicity, affecting 75/165 patients (45.5 %), followed by dysgeusia (n = 51, 30.9 %), alopecia (n = 41, 24.9 %), fatigue (n = 33, 20 %), and increased CPK (n = 17, 10.3 %). We compared the occurrence of AEs in the once-daily sonidegib cohort and in the every-other-day dose modification cohort: 13/66 (19.7 %) patients on the dose reduction schedule experienced at least one AE, and 62/99 (62.6 %) patients on the continuous regimen had at least one AE, p value < 0.0001 (Fig. 2A). For the every-other-day sonidegib cohort, we also investigated the occurrence of AEs before and after the switch to the dose modification schedule (results computed out of 60 patients who underwent the switch from once-daily to every-other-day sonidegib regimen): 42/60 (70 %) patients presented with at least one AE prior to the switch to the dose reduction regimen, and 13/60 (21.7 %) patients experienced one AE after the switch to the every-other-day sonidegib administration (p value <0.0001) (Fig. 2B).

Table 2
Patients' effectiveness outcomes, including best response by the end of follow-up period, duration of response and median progression free survival.

Response	Overall cohort N = 165	Continuous regimen N = 99	Dose reduction regimen N = 66
CR, N (%)	87 (52.7)	46 (46.5)	41 (62.1)
PR, N (%)	49 (29.7)	34 (34.3)	15 (22.7)
SD, N (%)	26 (15.8)	18 (18.2)	8 (12.2)
PD, N (%)	3 (1.8)	1 (1)	2 (3)
ORR, (95 % CI)	82.4 (87.5–75.9)	80.8 (87.4–72)	84.8 (91.6–74.3)
DOR (months), median (range)	6 (1–37)	9.5 (1–37)	6 (1–28)
PD after best response, N (%)	11 (6.6)	5 (5 %)	6 (9 %)
Median PFS (months) (95 % CI)	NE	NE	31 (19-NE)
FUP duration (months), median (range)	13 (1–47)	19 (1–47)	7 (1–38)

Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; FUP, follow-up; N, number; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

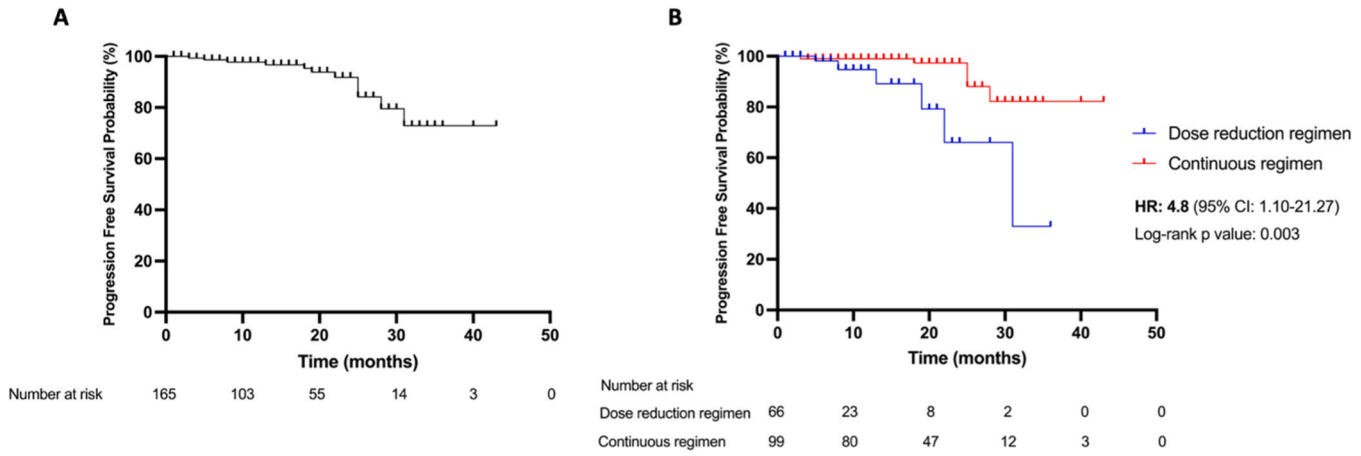

Fig. 1. Progression free survival probability for the overall cohort **(A);** for patients on sonidegib continuous regimen and dose-reduction regimen **(B).** Abbreviations: CI, confidence interval; HR, hazard ratio.

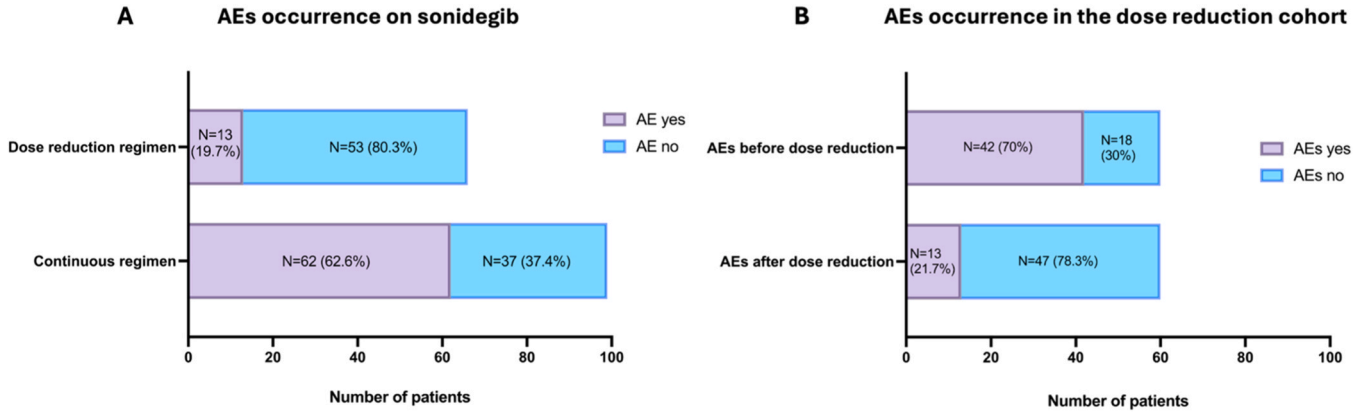

Fig. 2. AEs occurrence on sonidegib comparing the dose reduction regimen and the continuous regimen **(A);** AEs occurrence in the every-other-day sonidegib cohort before and after dose reduction (results computed out of 60 patients who underwent the switch from the once-daily to the every-other-day sonidegib regimen) **(B).** Abbreviations: AEs, adverse events; N, number.

Table 3
Univariate and multivariate logistic regression analysis investigating the probability of switching to sonidegib dose reduction regimen.

Variable	Crude OR	95 % CI	P-value	Adjusted OR	95 % CI	P-value
Age (years)	1.02	0.99–1.05	0.13	1.02	0.99–1.05	0.1
Gender						
Male	Ref	0.31–0.93	0.38	Ref	0.29–1.22	0.16
Female	0.55			0.6		
ECOG PS						
0–1	Ref	0.8–7.6	0.1	Ref	0.76–8.7	0.12
2–4	2.4			2.5		
Gorlin-Goltz syndrome						
No	Ref	0.19–1–9	0.44	/	/	/
Yes	0.6					
Occurrence of AEs						
No	Ref	0.6–2.3	0.6	/	/	/
Yes	1.2					
Number of AEs						
1–2	Ref	1.2–5	**0.01**	Ref	1.44–7.27	**0.004**
≥ 3	2.4			3.1		
CTCAE grade						
1–2	Ref	0.9–5.6	0.08	Ref	0.74–5.33	0.17
≥ 3	2.2			1.97		
CR achievement						
No	Ref	1.01–3.5	**0.04**	Ref	1.36–5.85	**0.004**
Yes	1.8			2.76		

Abbreviations: AEs, adverse events; CI, confidence interval; CR, complete response; CTCAE, common terminology criteria for adverse events; ECOG PS, eastern cooperative oncology group performance status; OR, odds ratio; Ref, reference

3.3. Predictors of switch to the every-other-day dose reduction schedule

We investigated patients' clinical factors associated with the probability of switch from the once-daily sonidegib administration to the every-other-day dose reduction schedule. Development of ≥ 3 AEs was significantly associated with an increased probability of undergoing sonidegib dose modification, according to our univariate and multivariate logistic regression model (OR: 3.1, 95 % CI: 1.44–7.27; p-value: 0.004) (Table 3). Conversely, neither the occurrence of at least one AE nor the CTCAE grade of AEs were significantly associated with the probability of switching to the every-other-day regimen. Patients achieving CR had a significantly higher probability of treatment modification from once-daily to every-other-day sonidegib administration, both at univariate and multivariate logistic regression analysis (OR: 2.76, 95 % CI: 1.36–5.85; p value 0.004) (Table 3).

4. Discussion

In the present study, we investigated the effectiveness and safety profile of sonidegib dose modification from the once-daily to the every-other-day regimen in an Italian cohort of laBCC patients; we also explored patients' clinical factors associated with the event of undergoing sonidegib dose reduction along treatment course.

Long-term management of aBCC patients on treatment with HHI is challenging, and the identification of strategies aiming at balancing treatment efficacy and tolerability are crucial for optimal disease control [11,12]. HHI dose modification schedules and treatment interruptions represent effective strategies to maximize patients' adherence to therapy and lead to sustained treatment duration [10]. Herein we presented data from a cohort of 165 laBCC patients on treatment with sonidegib, of whom 66 patients were on the every-other-day dose modification schedule. Sonidegib treatment duration was significantly longer in the dose reduction regimen cohort (median: 23 months) compared to the once-daily sonidegib administration cohort (median: 14 months), suggesting improved drug tolerability. The phase II randomized double-blind regimen-controlled MIKIE trial investigated two intermittent vismodegib regimens in patients with multiple BCCs, including Gorlin-Goltz syndrome [15]. Patients were randomized to treatment group A (12 weeks of 150 mg vismodegib per day, followed by 3 cycles of 8 weeks of placebo and 12 weeks of 150 mg vismodegib per day), and treatment group B (24 weeks of 150 mg vismodegib per day, followed by 3 cycles of 8 weeks of placebo and 8 weeks of 150 mg vismodegib per day). Both intermittent vismodegib schedules demonstrated prolonged therapy duration, with a median duration of treatment of 71.4 weeks and 68.4 weeks for arm A and B, respectively [15]. Data from the 42-month randomized double-blind phase II BOLT trial evaluated the impact of sonidegib dose reductions and interruptions in aBCC patients [16]. Investigators demonstrated a comparable efficacy profile for aBCC patients who did not experience sonidegib dose reductions/interruptions and patients who underwent at least one dose reduction/interruption along treatment course, with an ORR of 48.5 % (95 % CI: 36.0–61.1) and 46.2 % (95 % CI: 19.2–74.9), respectively [16]. Accordingly, in our study the effectiveness outcomes were comparable in the once-daily and in the every-other-day sonidegib cohorts, with an ORR of 80.8 % (95 % CI: 87.4–72) and 84.8 % (95 % CI: 91.6–74.3), respectively. Nevertheless, in our study, DOR and PFS probability were significantly reduced in the sonidegib dose reduction regimen compared to the continuous regimen, suggesting decreased disease control in the long-term. A few real-life retrospective studies assessed the effectiveness and safety profile of several different HHI dose modification schedules in a relatively small number of patients [17–20]. A single-center case series from Villani et al [20]. evaluated the effectiveness and safety profile of every-other-day sonidegib dose modification in 9 of 20 laBCC patients. Investigators reported similar clinical responses comparing the dose reduction regimen group and the daily dosing regimen group (6/9 CR and 3/9 PR in the dose modification cohort, and 6/11 CR and 3/11 PR in the once-daily cohort) [20].

In our cohort, CR achievement was the most common cause leading to sonidegib dose modification to the every-other-day schedule (46.6 %, n = 28). Also, CR achievement was significantly associated with a nearly 3-fold increased probability of switching to the dose reduction regimen, according to our univariate and multivariate logistic regression model (OR: 2.76, 95 % CI: 1.36–5.85; p value 0.004). Extending HHI treatment beyond CR achievement is a critical step for the maintenance of long-term disease remission, despite the limited drug tolerability [11,14]. The every-other-day sonidegib regimen seems a tolerable strategy that should be taken into account for laBCC patients on disease remission and at risk of tumor relapse. Indeed, our PFS rate was particularly higher compared to other real-life studies investigating laBCC progression after discontinuation of HHI, suggesting the importance of additional interventions after CR achievement as consolidation strategies [21,22]. The ongoing phase II open-label single-arm SONIBEC trial (NCT04806646) is investigating a tailored sonidegib dose modification schedule in laBCC patients who achieved CR after a course of once-daily sonidegib. Results from this trial are likely to provide further insights into the optimal sonidegib dose reduction schedule, combining long-term therapeutic efficacy and drug tolerability.

Concerning the safety profile, 65.5 % of our patient population experienced at least one AE, and 14.5 % had at least one grade ≥ 3 toxicity. The occurrence of AEs was significantly different between the continuous regimen cohort and the dose reduction cohort (62.6 % and 19.7 %, respectively; p value <0.0001). Furthermore, looking specifically at the every-other-day sonidegib group, the development of at least one AE was significantly reduced after the implementation of the dose reduction schedule (69.7 % of patients with at least 1 AE prior to treatment modification and 19.7 % of patients with at least 1 AE after treatment modification; p value <0.0001). In our study, development of AEs was the second cause leading to sonidegib dose modification (38.4 %, n = 23). Accordingly, the occurrence of ≥ 3 AEs was significantly associated with a 3-fold increased probability of switching to the every-other-day sonidegib schedule, underscoring the relevance of toxicities on the long-term treatment course. In the pivotal trials ERIVANCE and BOLT, AE occurrence led to treatment discontinuation in 21 % and 30 % of patients [8,9], respectively, highlighting the impact of AEs on the long-term disease management. A modified sonidegib treatment schedule seems a valuable approach combining a more tolerable AE profile with sustained treatment duration, ultimately leading to improved long-term disease control.

Six of the 66 patients on the dose reduction regimen were on every-other-day sonidegib from treatment start due to polypharmacy, and 9/60 (15 %) patients switched to the dose modification schedule due to development of comorbidities which required the introduction of new medications potentially interfering with HHI. Advanced BCC often affects fragile and elderly patients on several medications [23]; this population is routinely excluded from clinical trials. A few real-life case series suggest that HHI are safe and effective also in elderly patients with several comorbidities [24–27]. Notably, among the 6 patients who were on every-other-day sonidegib from treatment start, 3/6 and 3/6 achieved PR and SD, respectively, suggesting that the every-other-day schedule is feasible and effective also in patients on several concomitant medications.

5. Conclusion

Patients on the every-other-day dose modification schedule had comparable ORR, albeit with reduced DOR and PFS probability compared to the once-daily sonidegib cohort; the AE profile was milder in the dose reduction regimen group. Achievement of CR and occurrence of multiple AEs were significant predictors of treatment modification to the dose reduction schedule.

IRB approval status

This study protocol was reviewed and approved by the Ethical Committee of Università Cattolica del Sacro Cuore, approval number 3890.

CRediT authorship contribution statement

Vincenzo Maione: Supervision, Investigation. **Emi Dika:** Supervision, Investigation. **Ketty Peris:** Writing – review & editing, Supervision, Resources, Project administration. **Iris Zalaudek:** Supervision, Investigation. **Marco Palla:** Investigation. **Francesco Lacarrubba:** Supervision, Investigation. **Alessia Villani:** Investigation. **Pietro Quaglino:** Supervision, Investigation. **Claudia Costa:** Investigation. **Giuseppe Argenziano:** Supervision, Investigation. **Enrico Bocchino:** Investigation. **Vincenzo De Giorgi:** Supervision, Investigation. **Luca Bianchi:** Supervision, Investigation. **Maria Concetta Fargnoli:** Writing – review & editing, Supervision, Investigation. **Paola Queirolo:** Supervision, Investigation. **Paolo Antonio Ascierto:** Supervision, Investigation. **Massimiliano Scalvenzi:** Supervision, Investigation. **Giovanni Pellacani:** Supervision, Investigation. **Alessandro Di Stefani:** Supervision, Investigation. **Caterina Longo:** Supervision, Investigation. **Maria Mannino:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization.

Patient Consent

Written informed consent has been collected from participants in order to participate to the study.

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none

Declaration of Competing Interest

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