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Real-world experience with vismodegib and sonidegib in advanced basal cell carcinoma: a multicenter Italian study

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Boehringer-Ingelheim, Novartis, Pfizer, Sanofi and UCB; MA has served as an advisory board member, consultant and has received fees and speaker's honoraria or has participated in clinical trials for Helsinn, Recordati Rare diseases, Kyowa Kiri, Takeda, Almirall, Pierre Fabre, Cantabria, and Vivascope GmnB; GP has been a consultant and/or speaker for Pierre-Fabre, Jansenn, Abbvie; AC has been a consultant and/or speaker for AbbVie, Leo Pharma, Eli Lilly, Novartis, Janssen-Cilag, Amgen, Almirall, UCB Pharma and Boehringer Ingelheim. The other authors have no conflict of interest to declare.

Ethics approval and consent to participate: institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. All patients received sonidegib or vismodegib, as in good clinical practice, in accordance with European guidelines. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy. The participants provided their written informed consent to participate in this study.

Consent for publication: all included patients had provided written consent for a retrospective study of data collected during routine clinical practice (demographics, clinical scores).

Availability of data and materials: the datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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Abstract

Vismodegib and sonidegib are smoothened (SMO) inhibitors approved for the treatment of advanced basal cell carcinoma (aBCC). This study investigates the real-world experiences and outcomes associated with these therapies across multiple Italian centers.

A retrospective, observational, multicenter study was conducted. Medical records of patients with local advanced basal cell carcinoma (laBCC) treated with SMO inhibitors outside of clinical trials from July 2019 to April 2024 were analyzed.

A total of 57 patients were included in the study, with 19 (33.3%) receiving vismodegib and 38 (66.7%) receiving sonidegib. Vismodegib demonstrated a complete response (CR) in 31.6% of cases and a partial response (PR) in 26.3%. Sonidegib achieved a CR of 47.4% and a PR of 36.8%. The median treatment duration was 8 months for vismodegib and 12 months for sonidegib. Adverse events were more frequently reported with vismodegib. Treatment interruption due to adverse events occurred in 47.4% of vismodegib recipients and in 13.2% of those receiving sonidegib. The progression of the disease under treatment occurred in 7.9% of cases of patients under sonidegib and in 26.3% of cases under vismodegib.

Introduction

Basal cell carcinoma (BCC) is the most common malignant epithelial tumor in light-skinned Caucasian people (type 1 or type 2 skin phototypes). This skin tumor is the most common type of non-melanoma skin cancer (NMSC), and its incidence is steadily increasing worldwide as the average age and cumulative UV radiation exposure rise. Indeed, this skin cancer is the result of an aberrant proliferation of genetically damaged basal cells of the epidermis primarily induced by UV-light chronic exposure. The male-to-female ratio is currently around 2.1:1, and the highest incidence has been observed in subjects aged 60 to 70 years, with the highest rates found in Europe, Australia, and the United States.[1-3] The main risk factors involved in the development of this neoplasm include chronic sunlight exposure, immunosuppression, ionizing radiation, and chronic exposure to chemical agents such as arsenic, polycyclic aromatic hydrocarbons, and chlorophenols. However, an important role is also played by genetics, and this is demonstrated by some inherited cancer syndromes characterized by recurrent and recidivate BCC, such as xeroderma pigmentosum, Bazex-Dupré-Christol syndrome, albinism, and Gorlin syndrome.[1,2,4]

The aberrant activation of the classic hedgehog signaling pathway has a crucial role in the pathogenesis of BCC. This pathway involves the secretion of glycoproteins into the intercellular space, such as Sonic hedgehog (Shh), Indian hedgehog (Ihh), and Desert hedgehog (Dhh). Among these, Shh is the most

potent glycoprotein and typically binds to and inactivates the transmembrane protein Patched1 (*PTCH1*), allowing smoothened (SMO) to remain active. This induces a complex intracellular cascade that leads to the activation of three GLI transcription factors. GLI targets include genes involved in cell proliferation, apoptosis, angiogenesis, epithelial-mesenchymal transition, and stem cell self-renewal. The *PTCH1* loss-of-function mutations and secondarily activating mutations affecting *SMO* and *SUFU* genes are involved in most of the cases of BCCs.[3-6]

Although BCC is considered malignant due to its ability to invade nearby tissues, it is characterized by slow growth and local invasiveness, and typically, it doesn't metastasize to distant organs. This contributes to its generally favorable prognosis when compared to more aggressive forms of cancer. Specifically, its metastatic rate ranges from 0.0028% to 0.5%; in these cases, the 5-year survival rate is 10%.[2] However, sometimes BCCs could progress to advanced basal cell carcinomas (aBCCs), a clinically heterogeneous group of BCCs with local invasion and major tissue destruction (locally advanced basal cell carcinoma [laBCC]), or with rare instances of metastasis (metastatic basal cell carcinoma). The availability of effective therapeutic options is mandatory in challenging scenarios involving multiple, inoperable, or extensive lesions. Target therapies for the treatment of BCC have acquired considerable attention in recent years.[5]

For this reason, in patients with laBCC for whom surgery and/or radiotherapy are contraindicated or cannot achieve curative outcomes with acceptable results or in those who have metastatic disease, therapy with hedgehog inhibitors (HhIs) sonidegib and vismodegib is the first-line treatment.[3,4,7,8] Both vismodegib and sonidegib have received approval for the treatment of laBCC, which is not amenable to curative surgical or radiotherapeutic intervention.[2,3,9] In 2012, the Food and Drug Administration (FDA) approved the first drug, vismodegib, followed by approvals from the European Medicines Agency (EMA) and Agenzia Italiana del Farmaco (AIFA) a year later for the treatment of metastatic or inoperable aBCC.[10,11] Subsequently, in 2015, sonidegib received FDA approval, followed by approvals from the EMA and AIFA, for the treatment of laBCC in patients who are ineligible for curative surgery or radiotherapy.[12,13]

Extensive prospective clinical trials have demonstrated the safety and effectiveness of vismodegib and sonidegib. These trials have yielded promising results regarding tumor response rates, progression-free survival (PFS), and overall survival (OS) in patients with aBCC. The HhIs have demonstrated prolonged efficacy with long-lasting responses. Still, their durable treatment is often impeded by the low tolerability and the occurrence of several class-related adverse events (AEs), such as muscle spasms (54-71% for sonidegib and vismodegib respectively), dysgeusia and upper gastrointestinal discomfort (44-58%), hair loss (49-66%), fatigue (32-39%), and weight loss (44-56%). The results of

a *post hoc* analysis describing the time to onset and severity of treatment-emergent adverse events (TEAEs) in patients treated with the two HhIs, suggested a delayed onset of many common TEAEs and a lower incidence of muscle spasm, alopecia, and dysgeusia in patients treated with sonidegib compared with vismodegib.[14,15]

Studies into the pharmacokinetic profiles point out that sonidegib seems to be more lipophilic than vismodegib, with a volume of distribution of >9.000 L, indicating extensive distribution in the tissues; otherwise, vismodegib has a volume of distribution of 16-27 L, suggesting that it is largely confined to the plasma.[14,15] In theory, this evidence indicates that sonidegib is more distributed in the skin compared with vismodegib, which may potentially explain the differences in efficacy and toxicity observed in our real-life case series.[3,6,16] In the event of AEs, before considering switching to second-line immunotherapy, various strategies such as dose interruptions, on-label alternate-day dosing, and the use of supportive medications should attempt to enhance patient tolerability. However, the patients may avail of cemiplimab, recently approved as a second-line treatment for adult patients with aBCC, when developing progression while on HhIs therapy (due to primary or secondary resistance) or in case of persisting toxicity despite the failure of long-term management of AEs.[15-17]

The effectiveness and safety profile of sonidegib and vismodegib were studied in the pivotal phase II double-blind randomized (BOLT) and single-arm phase II (ERIVANCE) trials, respectively. A direct comparison between vismodegib and sonidegib in a randomized controlled clinical trial is currently not available. Still, the ERIVANCE and BOLT results have recently been considered appropriate for indirect comparison. ERIVANCE used the conventional RECIST to evaluate the activity and efficacy, while BOLT used the more stringent mRECIST in addition to a pre-planned sensitivity analysis using ERIVANCE-like criteria. In an indirect comparison of the two objective response rates (ORR) based on the same response criteria, there was a slight trend in favor of sonidegib (ORR 74.2% for sonidegib and 60.3% for vismodegib) but a similar complete response (CR) rate (28.8% for sonidegib and 31.7% for vismodegib). Moreover, sonidegib provided a long-lasting duration of response (DOR) and progression-free survival (PFS) of about 2 years after the beginning of therapy. Conversely, DOR and PFS calculated for vismodegib were below 1 year.[18,19]

This retrospective multi-centric study aims to analyze the differences in the efficacy and safety profiles of sonidegib and vismodegib in the daily practice treatment of laBCCs.

Materials and Methods

This retrospective multi-center study included patients affected by laBCCs treated for at least one month outside a clinical study with HhIs (vismodegib or sonidegib). The analyzed data come from the

electronic records of the following Italian hospitals: Humanitas Research Hospital (Rozzano, Milan), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan), ASST Papa Giovanni XXIII Hospital (Bergamo), San Raffaele Hospital (Milan) and San Gallicano Hospital (Rome). The time frame of the analysis was between July 2019 and April 2024.

Indication criteria for vismodegib and sonidegib therapy included:

- multiple sporadic BCCs;
- BCCs linked to genetic syndromes;
- laBCC ineligible for surgery and radiotherapy.

LaBCC could be candidates for HhIs due to:

- repeated recurrence after surgical procedures or imiquimod therapy with curative intent;
- expected considerable morbidity and deformity after surgery;
- severe comorbidities representing a contraindication to surgical intervention.

The characteristics of all patients, including age, gender, cardio-metabolic comorbidities, tumor site and size, type of BCC, affection by cutaneous genetic syndrome, type of HhI therapy dosing regimen (intermittent *vs.* continuous), adverse events, previous therapy, and concomitant treatment, were obtained from electronic medical records.

Institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. All patients received vismodegib or sonidegib as in good clinical practice, in accordance with European guidelines. All included patients had provided written consent for a retrospective study of data collected during routine clinical practice (demographics, clinical scores). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

Progression-free survival (PFS) was calculated from the diagnosis of BCC to local recurrence and/or metastatic event, while the overall survival (OS) was calculated from the diagnosis of BCC to the date of death and/or last follow-up. Kaplan-Meier survival plot was performed to estimate PFS and OS. Patients who were lost to follow-up or who were alive at the time of the last follow-up were censored at the date of their last follow-up.

Results

Epidemiological data of the treated groups

A total of 57 patients treated with HhIs (vismodegib 150 mg/daily or sonidegib 200 mg/daily) for at least one month have been included in the current analysis. Patients have been collected from July 2019

to March 2024. Among them, sonidegib was the current treatment in 38 patients (66.7%) and vismodegib in 19 (33.3%) patients. Among the sonidegib-treated group, four patients were previously treated with vismodegib (10.5%). The median age at starting HhI was 76 years, ranging between 41 and 90 years. Among patients, 30 were males (52.6%) and 27 were females (47.4%). Most patients (n=35; 61.4%) were previously treated with surgical intervention for other BCCs, while topical 5% imiquimod cream was used in 4 patients (7%) (Table 1). The indication for vismodegib and sonidegib in this patient population was for laBCC (n=36; 63.2%) and multiple BCC (n=21; 36.8%), with no cases of metastatic BCC. Out of 21 patients with multiple BCCs, 6 were affected by Gorlin-Goltz syndrome (28.6%) and 1 by Xeroderma Pigmentosum (4.8%). Regarding the anatomic location of primary BCC, the axial site (trunk/head and neck) was involved in 54 cases; specifically, the head/neck region was involved in 48 cases (84.2%) and the trunk in 6 cases (10.5%). Finally, the limbs were the primary site of BCC in only 3 cases (5.3%). Our cohort of patients represented a heterogeneous group regarding comorbidities, with cardio-metabolic diseases (arterial hypertension, ischemic cardiovascular diseases, arrhythmias, and diabetes) as the most representative (n=27; 47.4%) (Table 1). The most common concomitant medications were beta-blockers (n=7; 12.3%), anti-epileptics (n=3; 5.3%), and new oral anticoagulants (n=4; 7%).

Dosing regimen and adverse events

Vismodegib

All patients received a continuous dose of 150 mg/daily. The median duration of the treatment was 8 months (range 2-18 months). For these patients, the indications for the treatment were multiple BCCs in 7 cases and laBCCs in the remaining 12 cases. Seven patients (36.8%) showed a BCC ≥5 cm (Table 2). Among the treated patients, 9 (47.4%) interrupted the treatment due to adverse events (dysgeusia and muscular cramps) (Table 3).

Sonidegib

Among patients under treatment with sonidegib, 22 patients (57.9%) received continuous dosing of 200 mg (1 capsule daily). Sixteen patients (42.1%) started with a continuous dosage and then switched to an alternate dosage of 200 mg (1 capsule every other day) (Table 2). 8 patients switched dosing due to the onset of AEs (muscular cramps, dysgeusia, alopecia, nausea), while the other 8 switched dosing after achieving a complete response (CR) by decision of the multidisciplinary team, based on the clinical conditions and comorbidities of the patients, to avoid severe AEs and treatment discontinuation. The treatment was started for multiple BCCs in 14 cases (36.8%). A BCC with a dimension larger than 5 cm was detected in 10 cases (26.3%) (Table 2). Among patients treated with sonidegib, 3 patients (7.9%) interrupted the treatment due to disease progression, 5 due to serious

muscular cramps with increased creatine phosphokinase (CPK) (13.2%), and 2 due to patient decision (5.3%) (Table 3). The general median duration of the treatment was 12 months (range 1-30 months). To better compare the influence of the sonidegib dosing regimen on AEs, we further analyzed the data of patients with both continuous and intermittent therapy. Among patients who switched to the sonidegib alternate dosing regimen, all patients (100%) showed an improvement in AEs from week 4 to week 16, with a reduction of alopecia, dysgeusia, and muscular cramps. Indeed, among them, no patient interrupted the treatment.

Comparing the AEs between sonidegib and vismodegib, we found that dysgeusia was present in 5 patients under sonidegib and in 9 patients under vismodegib. Weight loss was reported in 2 patients with sonidegib and 4 patients under vismodegib, while alopecia was detected in three cases of vismodegib and two cases of sonidegib. Muscular cramps were detected in 12 patients under sonidegib and 12 patients under vismodegib. Generally, adverse events were more commonly reported in the vismodegib group than sonidegib one (Table 3).

Effectiveness in sonidegib

The best overall response was a CR in 18 patients (47.4%), a partial response (PR) in 14 cases (36.8%), stable disease in 3 cases, and progression of the disease in 3 cases. The median PFS was 22 months (range 2-103 months) (Figure 1).

Effectiveness in vismodegib

The best overall response was a CR in 6 patients (31.6%), a PR in 5 cases (26.3%), a stable disease in 3 patients, and progression of the disease in 5 patients. The median PFS was 13 months (ranging between 1 and 26 months) (Figure 1).

Switch from vismodegib to sonidegib

Four patients with laBCC were switched from vismodegib 150 mg/daily to sonidegib 200 mg/daily due to side effects. All the switched patients showed improvement in the AEs and achieved a PR.

Discussion

LaBCC or multiple basal cell carcinomas represent a significant challenge in management due to their aggressive nature and potential for recurrence. Considering that the dysregulation of the hedgehog signaling pathway plays a prominent role in BCC's pathogenesis, HhIs have emerged as a potential therapeutic option in treating this neoplasm.

Specifically, HhIs, such as vismodegib and sonidegib, target the aberrant hedgehog signaling by inhibiting the smoothened receptor, showing great outcomes in managing laBCC and multiple BCCs in clinical trials. Phase 2 BOLT trial reported a median overall survival of 5 years in patients treated

with sonidegib, and a CR of 21% and PR of 39.4% (RECIST-like criteria), while ERIVANCE study reported a CR between 5% and 12% and a PR rate between 30% and 45% with vismodegib.[18,19] However, to date, only two articles have compared sonidegib and vismodegib.[5,20] A higher tissue penetration and higher concentration of sonidegib on the skin have been shown by a pharmacokinetic study performed by Dummer *et al.*[15] However, these data have some biases due to the small number of patients and short observational period. Therefore, more comparative studies between vismodegib and sonidegib will always be needed to better evaluate the differences between these two treatments.

Our 5-year real-life retrospective multicenter study highlights the response and limitations of HhIs in laBCC patients. Our population was heterogeneous and was mainly characterized by laBCC and patients with multiple BCC, without cases of metastatic BCC. Due to the high median age, most patients showed cardiovascular comorbidities. Contrary to the registrative studies ERIVANCE and BOLT, 36.8% of patients showed multiple BCC in our analysis. As reported also by Grossmann *et al.*, patients with genetic syndromes, as well as patients with multiple BCC, are increasingly reluctant to perform surgical interventions, and finding alternative non-surgical therapies significantly improves their quality of life.[1] Interestingly, 31 out of 37 patients (83.8%) with multiple BCC showed a genetic syndrome (Gorlin-Goltz and Xeroderma Pigmentosum).

Our data confirm the antitumoral efficacy of HhIs, with only 7.9% of patients under sonidegib and 26.3% of patients under vismodegib showing a disease progression. However, AEs may arise in HhI patients and sometimes may be the cause of discontinued therapy. Specifically, we found that muscular cramps were the most common side effects in both sonidegib and vismodegib-treated groups. However, there were some differences: while 47.4% of vismodegib patients had their treatment interrupted due to muscular cramps that reduced their quality of life, only 13% of sonidegib patients had their treatment interrupted due to muscular cramps associated with dysgeusia or alopecia. Therefore, a switch from vismodegib to sonidegib was needed.

There is some data in the literature reporting an improvement of muscular spasms and cramps with quinine sulfate (200-250 mg twice a day), as well as some patients may also benefit from peroral magnesium or muscle relaxants such as tizanidine.[1] Certainly, the possibility of performing an alternating regimen with sonidegib allows a reduction in the incidence of AEs and also justifies the reason why, in our sample, patients with sonidegib were the majority. Contrariwise to Grossmann *et al.*, in our sample, weight loss and alopecia did not significantly impact therapeutic continuation.

Regarding the therapeutic regimen, 42.1% of patients treated with sonidegib performed an alternate dosing regimen, while all patients treated with vismodegib performed a continuous regimen. Among patients who switched to a sonidegib-alternate regimen, all patients showed an improvement in AEs

from week 4 to week 16, with a reduction of alopecia, dysgeusia, and muscular cramps. Furthermore, the alternate regimen improved treatment tolerability, allowing for long-term treatment, particularly in patients with genetic syndromes and multiple BCC. Unfortunately, our sample's limited number of patients did not allow us to carry out a specific analysis to compare more significant differences between patients with continuum or alternate regimens.

In some cases (7.9% among sonidegib and 26.3% among vismodegib-treated group), a disease progression was detected. In these cases, an anti-PD1 treatment with cemiplimab can be offered to this subgroup of patients, as it was approved by the FDA and EMA.[21]

Conclusions

HhIs propose a noninvasive therapeutic option for patients who are not suitable for surgery due to comorbidities or concomitant medications. Moreover, they can avoid extensive surgical interventions that significantly impact aesthetic components, especially on the face/scalp area.

HhIs are the "game-changers" in the management of laBCCs and multiple BCCs, offering new therapeutic perspectives for patients with these challenging conditions. However, there are still some issues to be addressed, such as side effects and treatment resistance, to improve the prognosis of our patients. In this context, our study did show a better safety profile and greater effectiveness with sonidegib. However, due to the retrospective nature of the study and the limited number of analyzed subjects, further research is needed to tailor the treatment, avoid drug resistance, and optimize therapeutic response.

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Table 1. Patient baselines of the sample.

		N(%)	
Gender	Male	30	52,6
	Female	27	47,4
Anatomic site	Axial	54	94,7
	Limbs	3	5,3
Cutaneus Genetic syndroms	Gorlin Goltx	6	28,6
	XP	1	4,8
Prevoius therapy	Surgery	35	61,4
	Imiquimod	4	7
	Vismodegib	4	16
Cardio-metabolic comorbities		27	47,4

Table 2. Clinical features in sonidegib and vismodegib groups.

		N (%)			
		Sonidegib		Vismodegib	
Dose regimen	**Continuous**	22	57.9	19	33.3
	Alternate	16	42.1	-	-
Type BCC	**LaBCC**	24	63.2	12	63.2
	Multiple	14	36.8	7	36.8
Dimension	**<5cm**	28	73.6	12	63.2
	≥5cm	10	26.3	7	36.8

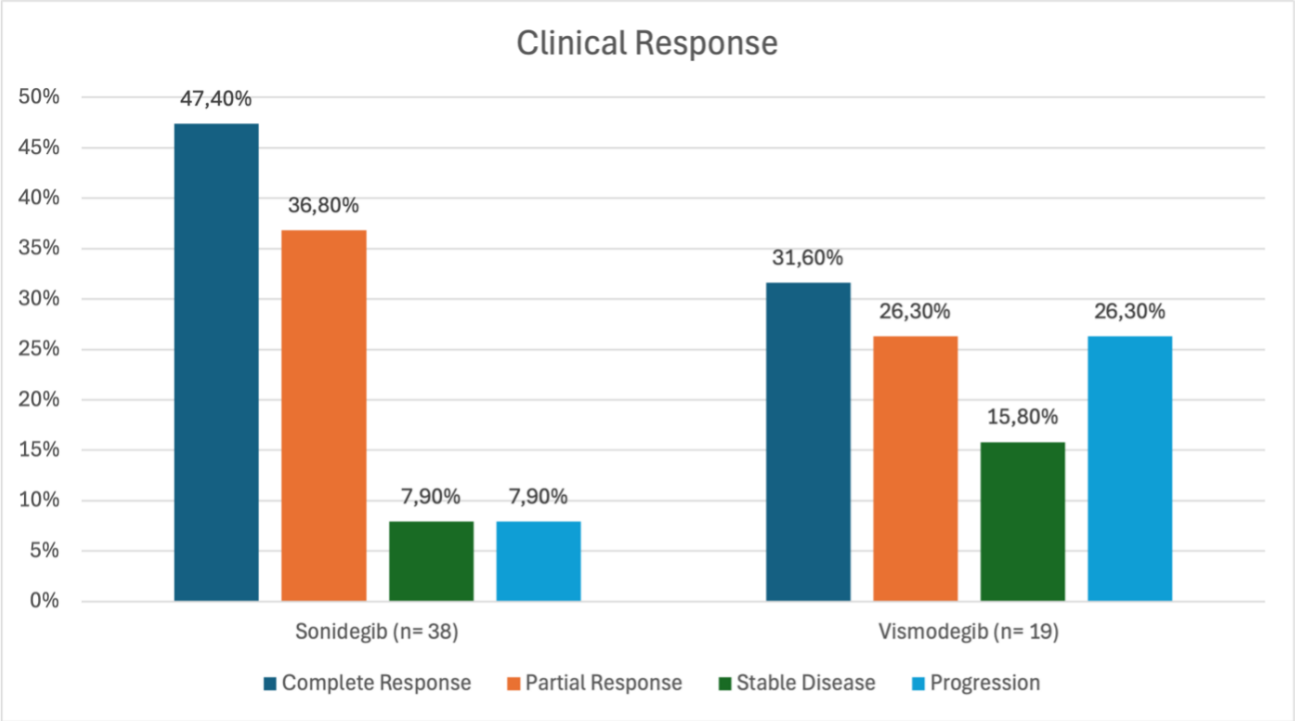
laBCC, local advanced basal cell carcinoma.

Table 3. Reported adverse events during the treatment with sonidegib and vismodegib in our cohort of study.

AE	Sonidegib (n=38)	Vismodegib (n=19)
Muscular cramps	12 (31.6%)	12 (63.2%)
Dysgeusia	5 (13.2%)	9 (47.4%)
Weight loss	2 (5.3%)	4 (21.1%)
Alopecia	2 (5.3%)	3 (15.8%)

AE, adverse events.

Figure 1. Effectiveness outcomes of sonidegib and vismodegib-treated cohort study.



Appendix authors list

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