ORIGINAL ARTICLE

Analysis of efficacy and safety of vismodegib therapy in patients with advanced basal cell carcinoma – real world multicenter cohort study

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Abstract

Background Basal cell carcinoma (BCC) is the most frequent non-melanoma skin cancer. The basis of treatment is surgical resection. The treatment of locally advanced and metastatic disease is currently based on sonidegb or vismodegib, small molecule inhibitors of the hedgehog signalling pathway.

Objectives The study aimed to retrospectively analyse the efficacy and safety of treatment with vismodegib in 108 patients with locally advanced or metastatic disease treated from August 1st, 2017 to December 31st, 2020. The primary objective was to evaluate the objective response rate (ORR), overall survival (OS) and progression-free survival rates. The secondary aims of the study were the disease control rate, the incidence of adverse events (AEs) and the estimation of the factors that potentially impact the treatment outcome and patient survival.

Methods Patients treated in national drug programme were enrolled into this retrospective cohort study. Evaluation of the treatment efficacy was performed according to CT/MRI scans and by the response evaluation criteria in solid tumours (RECIST) 1.1. The safety evaluation was performed according to the Common Terminology Criteria for Adverse Events v. 5.0 (CTCAE) classification and severity assessment.

Results The median duration of treatment was 14 months (range 1–94 months). The median progression-free survival reached 30.5 months (95% CI; 24.8–36.3), and the progression-free survival rate after 6, 12 and 24-months were 92%, 78% and 61%, respectively. The median overall survival was 41.5 months (95% CI; 31.6–51.3), and the overall survival rate after 1, 2 and 3 years accordingly 86%, 73% and 60%. The univariant and multivariant analysis indicated that the female gender is an independent positive prognostic factor of progression-free survival.

Conclusions The response to treatment is the prognostic factor for response maintenance and better overall survival. The therapy was well tolerated with the safety profile consistent in general with known from previous studies.

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Conflicts of Interest

MS received honoraria for lectures from Roche, Novartis, Tekeda, Sanofi, Medac and BMS; , honoraria for participation in advisory meetings from BMS, Novartis and Takeda; and financial support for participation in conferences from Roche,

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Introduction

Basal cell carcinoma (BCC) accounts for approximately 80% of all non-melanoma skin cancers and, despite its high incidence, is characterized by low mortality rates.[1,2] The mainstay of treatment is surgical resection or radiotherapy.[2,3] Therapy of locally advanced/inoperable and metastatic disease is currently based on treatment with hedgehog (Hh) inhibitors (vismodegib, sonidegib).[2,3]

The Hh signalling pathway is an important regulator of cell growth and differentiation. It is inactive in most normal adult tissues. The reactivation of the Hh pathway is involved in the pathogenesis of several malignancies, including BCC.[1,2] The transmembrane receptor patched (PTCH) is a negative regulator of the transmembrane receptor smoothened (SMO). PTCH is the receptor for the Hh ligand and inhibits SMO until the Hh ligand binds, allowing SMO to signal. Vismodegib is a small molecule inhibitor of SMO, a key component of the Hh signalling pathway.[2] Vismodegib was approved in the United States in January 2012 and the European Union in July 2013 for the treatment of locally advanced basal cell carcinoma (laBCC), not eligible for surgery or radiotherapy and metastatic basal cell carcinoma (mBCC).[2]

The efficacy and safety of vismodegib have been shown in phase I and phase II clinical trials and confirmed in clinical practice.[2,4–15] In Poland, therapy with vismodegib has been available in the national drug programme since August 1st, 2017, and sonidegib has been approved but is not reimbursed.

This study presents the real-world setting-based data of treatment outcomes and safety in 108 patients treated under the national drug programme in selected centres. The primary objective was to evaluate the objective response rate (ORR), overall survival (OS) and progression-free survival (PFS) rates according to Response Evaluation Criteria In Solid Tumours (RECIST) v 1.1.[16] The secondary aims of the study were the disease control rate, the incidence of adverse events (AEs) and the estimation of the factors that potentially impact the treatment outcome and patient survival. As far as we know, this is one of the largest studies published to date, the results of which have been compared with those of the ERIVANCE and STEVIE studies.[4–14]

Materials and methods

Data collection

The investigation was designed as the multicentre retrospective cohort study, which enrolled 108 out of 182 patients included in the national drug programme of vismodegib treatment between August 1st, 2017 and December 31st, 2020, with a minimum 6-month follow-up from the beginning of treatment. All patients fulfilled the directions of the national drug programme and uniform eligibility criteria and follow-up.[17] The medical records came from six hospitals, which were leaders in patients recruiting.

Inclusion and exclusion criteria

Patients classified to vismodegib treatment in the national drug programme fulfilled the standard inclusion criteria: had mBCC, defined as histologic confirmation of BCC with presence of distant metastasis (e.g. lung, liver, lymph nodes or bone), confirmed by computerized tomography or magnetic resonance imaging, or had laBCC, defined as histologically confirmed disease that is considered to carcinoma inappropriate for surgery or radiotherapy or has a medical contraindication to surgery and radiotherapy, or BCC that has recurred in the same location after two or more surgical procedures and curative resection is deemed unlikely or anticipated substantial morbidity and/or deformity from surgery. Exclusion criteria were age < 18 years, pregnancy and lactation, ECOG >2, the coexistence of other malignant neoplasms, that is the condition after treatment or under palliative treatment (regardless of the response to treatment), or failure to achieve complete remission after radical treatment; not adequate organ function determined based on laboratory blood tests, hypersensitivity to the active substance or any of the excipients; non-compliance with the recommendations of the pregnancy prevention programme by women of childbearing age and men or the presence of other contraindications to the use of vismodegib contained in the current Summary of Product Characteristics.[16,18]

Intervention

All patients received vismodegib (Erivedge) 150 mg/day p.o. until disease progression, unacceptable toxicity or treatment discontinuation.[19] The patients were assessed upon the directions of the national drug programme.[17] The visit schedule: first monitoring visit six weeks after the first dose of vismodegib, next visits within no longer than eight weeks intervals. During each visit, photographic documentation with visible scale, laboratory tests, CT/RMI scans (if necessary in the opinion of the leading specialist) and AEs assessments were performed.

Definitions

The treatment efficacy was evaluated by PFS, OS, overall response rate (ORR) and disease control rate (DCR) defined by the RECIST 1.1.[16] The PFS was defined from the first administration of medication (day 1) until disease progression according to RECIST, death from any cause, or last documented/reported visit. OS was defined as the time from the first drug administration to death from any cause or last documented visit. Duration of treatment was calculated as the time from first dose to treatment discontinuation due to any reason. In patients who were alive or continued treatment on December 31, 2020, the data were censored at the date of the latest evaluation visit. ORR was recorded as complete (CR) or partial response (PR). The treatment response of 5 patients who, during the treatment with vismodegib, had additional treatment introduced (radiotherapy, surgical excision, photodynamic therapy) were assessed before this intervention.

The safety evaluation was performed upon the data of reported AEs according to the Common Terminology Criteria for Adverse Events v. 5.0 (CTCAE) classification and severity assessment.[20]

Statistical analysis

Continuous variables were reported as mean and range for normal distributed or with median and interquartile range when distribution was skewed. Discrete variables were summarized as numbers and percentages. Chi-square, Fishers exact test, student's t-test and Mann–Whitney *U* test were used for between group comparisons. Median survival times were estimated by the Kaplan–Meier method. Kaplan–Meier estimator with the log-rank test was used for assessing and plotting the differences between survival curves. All factors with $P < 0.1$ in the univariate analysis were included in the multivariate Cox proportional hazard model. With all point estimates, 95% confidence intervals (CI) were reported. No adjustment for multiple testing was performed. The differences were considered statistically significant if the *P*-value was <0.05. All analyses and figures drawing were performed using IBM SPSS Statistics for Windows version 26 (IBM Corp).

Results

Patients

The study included 108 patients diagnosed with laBCC ($n = 95$, 88%) or mBCC ($n = 13$, 12%) treated with at least 1 dose of vismodegib (ITT population). The median age at the initiation of therapy was 71 years, and a male gender predominance was observed. All patients adjusted to the scheduled plan of visits with the first follow-up visit six weeks after the first dose of vismodegib and the next visits within eight weeks intervals.[17,19] During each visit, photographic documentation with visible scale, laboratory tests, and AEs assessments were performed. The CT/RMI scans were performed on each visit till the progression or, in case of complete response, repeated with the frequency based on the discretion of the leading specialist[17] 70.4% of patients prior to vismodegib treatment underwent multiple

surgical excisions. 29.6% of patients received radiotherapy, and 24.1% were treatment naïve. The detailed patient characteristic is presented in Table 1.

Outcomes

All patients have received at least one dose of vismodegib. The median follow-up was 16.9 months (1–85 months), with the median duration of exposure to vismodegib 14 months (1–94 months). At the time of data cut-off, 88.9% of patients were treated with vismodegib for at least 6 months (n = 96), 55.6% of pts (n = 60) continue treatment. 44.4% of patients discontinued therapy, mostly due to the disease progression (52.1%) or death (25%). The adverse AE were rarely (4.2%) the reason for treatment discontinuation (Table 2). The overall response rate (ORR) was 67.6%. The complete response (CR) achieved 17.6% of patients, 6.5% had progression of disease (PD) as their best response. The disease control rate (DCR) was 93.5% (Table 2).

The disease progression occurred in 40.7% of patients. The median PFS was 30.5 months (95%CI 24.8–36.3) with 1-year and 2-year PFS rates of 78% and 61%, respectively (Fig. 1a). By the time of the database lock, 31 patients (28.7%) died. The median OS was 41.5 months (95%CI 31.6–51.3) with a 1-year, 2-year and 3-year OS rates of 86%, 73% and 60%, respectively (Fig. 1b).

Table 1 Summary of baseline patient characteristics

Study population – patients with laBCC/mBCC treated with at least 1 dose of vismodegib (ITT)		***N* (%) *n* = 108 patients**
Age	Median (range) [years]	71 (35–94)
Gender	Female	43 (39.8)
	Male	65 (60.2)
Stage	Locally advanced BCC	95 (88.0)
	Metastatic BCC	13 (12)
Location of metastases	Lungs	8 (61.5)
	Bones	3 (23.1)
	Central Nervous system	1 (7.7)
	Skin	2 (15.4)
	Lymph nodes	2 (15.4)
Location of primary tumour	Cerebrocranium	49 (45.4)
	Face	8 (7.4)
	Large lesion affecting cerebrocranium and face	21 (19.4)
	Trunk	3 (2.8)
	Upper extremities	6 (5.6)
	Large lesion affecting more than one region	10 (10.2)
	Unknown	1 (0.9)
	Multiple (Gorlin – Goltz Syndrome)	9 (8.3)
Gorlin – Goltz Syndrome	(included in laBCC)	9 (8.3)
Previous treatment	Surgery	76 (70.4)
	Radiotherapy	32 (29.6)
	Chemotherapy	3 (2.8)
	None	26 (24.1)

Prognostic factors

The univariate analysis of factors potentially impacting the PFS has revealed significant ($P < 0.05$) differences depending on the gender and previous use of radiotherapy (Table 3). The multivariate analysis has confirmed that female gender is the only independent positive factor associated with PFS (HR 0.45; 95% CI 0.22–0.91; P = 0.026; Fig. 2).

Statistically significant prognostic factors impacting the OS in the univariate analysis were the best response to vismodegib and underlying Gorlin-Goltz syndrome (Table 3). Upon the multivariate analysis, only complete or PR to vismodegib were independent prognostic factors with HR of 0.05 (95%CI 0.01–0.48, P = 0.009) for patients with CR and 0.27 (95%CI 0.08–0.74, P = 0.014) for PR in reference to patients with PD (Fig. 3, Table 4).

The analysis of the Kaplan–Meier curves for OS, stratified by the best response (Fig. 3), pointed out their early separation between 6 and 12 months. Thus, further explorative analysis was performed of the long-term survivors (defined as patients treated with vismodegib for 12 months or more) and short–term (less than 12 months) treated patients. The long-term treatment group included significantly younger patients (median age 69 vs 76 years, P = 0.023), and was characterized by a good survival prognosis (no OS vs 14.57 months; $P < 0.001$, Fig. 4), a higher incidence of CR (27.8% vs 4.3%; $P < 0.001$) and a lower

Table 2 The treatment outcomes of the overall study group

		***N* (%) *n* = 108 patients**
Exposure to vismodegib	Median (range) [month]	14 [1–94]
	<6 months	12 (11.1)
	≥6 months	96 (88.9)
The best response to treatment according to RECIST v.1.1.	CR	19/ (17.6)
	PR	54/ (50.0)
	SD	28 (25.9)
	PD	7 (6.5)
	ORR	73 (67.6)
	DCR	101 (93.5)
Status of patients at the moment of database lock	Continue vismodegib treatment	60 (55.6)
	Alife – in observation/other treatment	17 (15.7)
	Deceased	31 (28.7)
Reasons for treatment discontinuation	Disease progression	25/48 (52.1)
	Adverse events	2/48 (4.2)
	Death	12/48 (25.0)
	Other	8/48 (16.7)

CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; PD, progression of the disease; SD, stable disease.

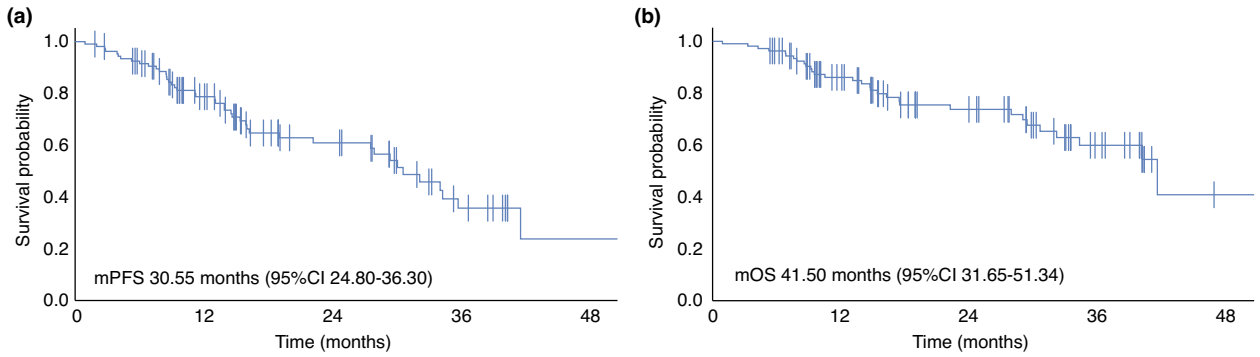

Figure 1 The results of the Kaplan–Meier analysis presented by the curves of the PFS (a) and the OS (b) in the ITT patients.

Table 3 The univariate and multivariate analysis of factors associated with PFS in patients with BCC treated with vismodegib

Factor		Median PFS (95%CI), months	*P* (log-rank)	HR (95% CI)	*P*
Gender	Male	27.8 (11.0–22.7)	**0.01**	1 (Ref.)	**0.026**
	Female	64 (NR–NR)		0.4 (0.2–0.9)	
Age	≤72	32.1 (25.9–38.3)	0.268		
	>72	27.8 (13.2–42.5)			
Stage	laBCC	30.5 (23.9–37.2)	0.087		
	mBBC	13.0 (6.3–19.7)			
Previous surgery	No	27.8 (10.3–45.4)	0.828		
	Yes	32.1 (27–37.2)			
Previous radiotherapy	No	32.1 (27.2–37.0)	**0.047**	1 (Ref.)	0.134
	Yes	16.0 (0.8–31.2)		1.6 (0.9–2.9)	
Gorlin-Goltz Syndrome	No	29.3 (20.5–38.1)	0.145		
	Yes	64.0 (NR–NR)			

Bold values indicates statistically significant.
95% confidence interval (95%CI); BCC, basal cell carcinoma; HR, hazard ratio; laBCC – locally advanced BCC; mBCC, metastatic BCC; NR, not reached; $P < 0.05$ considered statistically significant; PFS, progression-free survival.

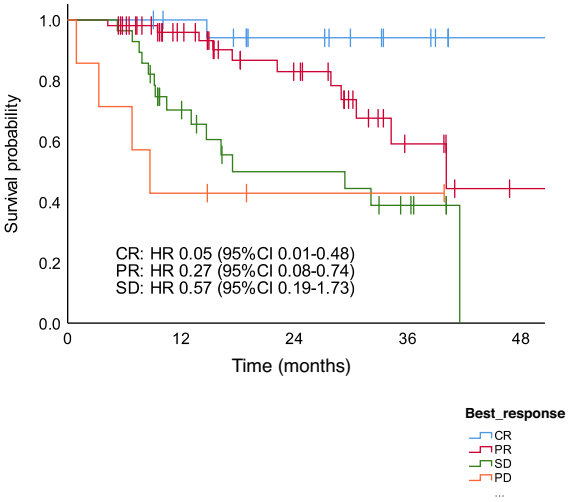

Figure 3 The Kaplan–Meier curve of the OS stratified by the treatment response assessed according to RECIST 1.1 criteria.

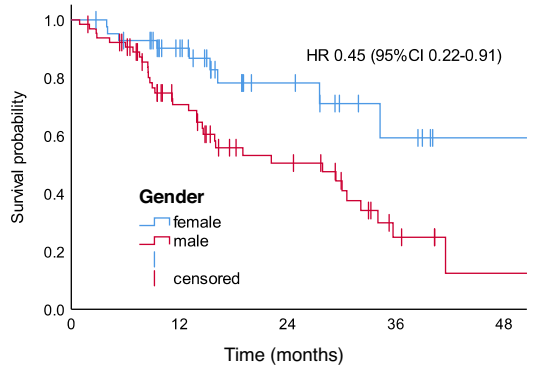

Figure 2 The Kaplan–Meier curve of the PFS stratified by gender.

probability of treatment discontinuation for any reason (34.4% vs 57.4%; $P = 0.017$;Table 5, Fig. 5).

Safety

83.3% of patients ($n = 90$) have experienced any adverse event (AE) associated with the vismodegib, while 48.1% had more than 1 AE ($n = 52$). The most common AE were alopecia observed in 48.1% of patients ($n = 52$) followed by muscle spasms reported by 38.9% of patients ($n = 42$), decreased appetite (33.3%, $n = 36$) and dysgeusia (26.9%, $n = 29$; Table 6). Most AEs were mild, as only 2.7% appeared of grade 3 or 4 toxicity. The safety profile has been summarized in Table 6. Rarely (4.2%), AE was the reason for treatment discontinuation (Table 2). The retrospective character of this study could have

Table 4 The univariate and multivariate analysis of factors associated with OS in patients with BCC treated with vismodegib

Factor		Median OS (95%CI)	*P* (log-rank)	HR (95% CI)	*P*
Gender	Male	40.08 (32.3–47.9)	0.059		
	Female	NR (NR–NR)			
Age	≤72	NR (NR–NR)	0.068		
	>72	34.2 (25.6–42.8)			
Stage	laBCC	41.5 (NR–NR)	0.366		
	mBBC	40.0 (28.3–51.9)			
Previous surgery	No	NR (NR–NR)	0.864		
	Yes	41.5 (31.9–51.0)			
Previous radiotherapy	No	NR (NR–NR)	0.085		
	Yes	34.2 (26.6–41.9)			
Gorlin-Goltz Syndrome	No	40.0 (34.9–45.7)	**0.040**	1	
	Yes	NR (NR–NR)		0 (NR–NR)	0.976
Best response to vismdegib	PD	8.7 (3.8–13.6)	**<0.001**	1 (Ref.)	
	SD	17.4 (0–42.2)		0.6 (0.2–1.7)	0.321
	PR	40.1 (28.1–52.1)		0.3 (0.1–0.7)	**0.014**
	CR	NR (NR–NR)		0.05 (0.0–0.5)	**0.009**

Bold values indicates statistically significant.
CI, confidence interval; CR, complete response; HR, hazard ratio; laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reached; OS, overall survival; *P*, *P*-value; PD, progression of disease; PR, partial response; SD, stable disease.

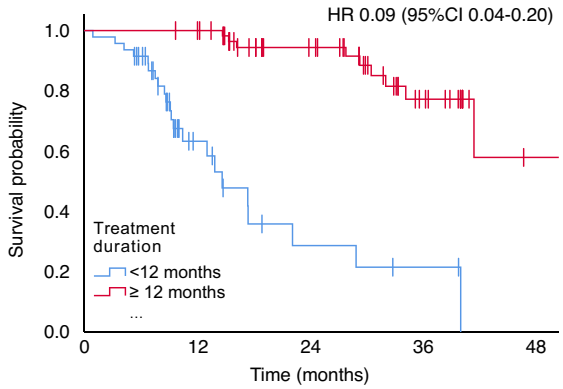

Figure 4 The Kaplan–Meier curve of the OS stratified by the duration of treatment: the short-term (<12 months) versus the long-term (≥12 months) exposure to vismodegib.

an impact on patients' reporting of AE symptoms (as most were subjective) and under-reporting in the medical records.

Discussion

In recent years, a meta-analysis, systematic reviews and results of studies based on national registries have been published, summarizing the efficacy and safety of Hh-pathway inhibitors, most of which related to the use of vismodegib in patients with laBCC.[2,4–8,14] Xie *et al.* performed a meta-analysis of efficacy based on 16 articles and showed that in laBCC, overall response rates (ORRs) were similar for vismodegib and sonidegib (69% vs. 57%, respectively) but not CR rates (31% vs. 3%, respectively).[4] In metastatic disease, the ORR of vismodegib was 2.7-fold higher than the ORR of sonidegib (39% vs. 15% respectively).[4] Publications analysing the effectiveness and safety of vismodegib treatment confirmed the results of the ERIVACE and STEVIE studies, even though they differed in the size of the sample and the duration of the study.[2,4,5,7,10–15]

The median duration of treatment in our study was 14 months (1–94 months), which stays in line with treatment duration in the ERIVANCE study, where median time was 12.9 months in mBCC and 12.7 months in laBCC group.[2,4,5,7,10–12] The median PFS reached 30.55 months, compared to 9.3 months in patients with mBCC and 12.9 months in those with laBCC in the ERIVANCE study and 13.1 months for mBCC patients and 23.2 months for laBCC patients in the STEVIE study.[2,4,5,7,10–15] The results of our study and the result of ERIVANCE and STEVIE studies are summarized in Table 7.

Regarding OS, 1- and 2- year rates were 86% and 73%, respectively, which correspond to the data reported in the ERIVANCE trial, where those rates were 78.7% and 62.3% in mBCC or 93.2% and 85.5% in laBCC, respectively (Table 7).[2,4,5,7,10–12] The ORR was used as a primary endpoint in registration trials with vismodegib. In the updated analysis of the ERIVANCE study, ORR based on central review was 47.6% (95% CI: 35.5–60.6) at 21-month follow-up, while the investigator-assessed ORR was 48.5% in the mBCC group (all PR) and 60.3% in the laBCC group.[2,4,5,7,10-11] In the STEVIE trial, response rates based on the investigator's assessment were 68.5% (95% CI 65.7–71.3) in laBCC patients and 36.9% (95% CI 26.6–48.1) in mBCC patients (Table 7).[2,4,5,7,13–15] In our retrospective analyses, the ORR for the whole population was 67.6%, consistently with

Table 5 Comparison of patients treated with VIS <12 months and ≥12 months

Factor		Patients treated with VIS <12 months *N* (%) *n* = 47	Patients treated with VIS ≥12 months *N* (%) *n* = 61	*P*
Age	Median (range) [years]	76 (43–94)	69 (35–92)	**0.023**
Gender	Female	14 (29.8)	29 (47.5)	0.063
	Male	33 (70.2)	32 (52.5)	
Stage	laBCC	40 (85.1)	55 (90.2)	0.423
	mBCC	7 (14.9)	6 (9.8)	
Gorlin – Goltz Syndrome		3 (6.4)	6 (9.8)	0.391
Previous treatment	Surgery	30 (63.8)	46 (75.4)	0.191
	Radiotherapy	16 (34.0)	16 (26.2)	0.378
	Chemotherapy	1 (2.1)	2 (3.3)	0.598
	None	14 (29.8)	12 (19.7)	0.223
The best response to treatment according to RECIST v.1.1.	CR	2 (4.3)	17 (27.8)	**<0.001**
	PR	22 (46.8)	32 (52.5)	
	SD	16 (34.0)	12 (19.7)	
	PD	7 (14.9)	0 (0)	
	ORR	24 (51.1)	49 (80.3)	
	DCR	40 (84.1)	61 (100)	
Treatment discontinuation		27 (57.4)	21 (34.4)	**0.017**
Reason for treatment discontinuation	PD	16 (59.3)	12 (57.1)	1.0
	AE	1 (3.7)	1 (4.8)	
	Death	2 (7.4)	2 (9.5)	
	Other	8 (29.6)	6 (28.6)	
Overall survival *N* = 108	Median (95%CI)	14.67 (9.59–16.78)	NR (NR-NR)	**<0.001**
Status of patients at the moment of database lock	Continue vismodegib	20 (42.6)	40 (65.6)	**0.001**
	Alive – in observation/other treatment	5 (10.6)	12 (19.7)	
	Death	22 (46.8)	9 (14.8)	

Bold values indicates statistically significant.
AE, adverse event; CR, complete response; DCR, disease control rate; laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reached; ORR, overall response rate; *P*, *P*-value; PD, progression of disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VIS, vismodegib.

previously published data. Importantly, over 90% of patients experienced disease control. Also, data from real-life analyses, such as RegiSONIC (NCT01604252) registry, reported a similar ORR – 68%.[4,21] The open-label, multicentre expanded access study (EAS) in patients with advanced BCC not eligible for radiotherapy or surgery reported slightly lower rates – 46.4% in laBCC and 30.8% in the mBCC cohort.[4,5]

Herms *et al.* analysed the baseline factors associated with relapse-free survival (RFS), OS and assessment of treatment modalities after relapse and their efficacy during follow-up of patients with complete remission of laBCC after vismodegib discontinuation.[9] The authors found RFS rate at 36 months was 35.4% (95% CI, 22.5% to 47.9%) for the total population and 40% (95% CI, 25.7% to 53.7%) for patients without Gorlin syndrome.[9] LaBCC to the limbs and trunk was the only variable independently associated with a higher risk of relapse (hazard ratio, 2.77; 95% CI, 1.23 to 6.22; $P = 0.019$).[9] Twenty-seven patients (50%) who experienced relapse during follow-up were retreated with vismodegib, with an objective response in 23 (ORR, 85%; CR rate, 37%; PR rate, 48%) and eligibility for surgery in 24 (42%).[9] Our secondary objective has also searched for potential predictive and prognostic factors affecting PFS and OS. Female gender was the only factor positively correlated with longer PFS. As far as we know, this is the first study to report such correlation, thus it requires confirmation in broader analyses. As per available data, gender did not appear to affect the pharmacokinetics of vismodegib, and our finding cannot be attributed to pharmacokinetics.[22]

Regarding OS, patients who achieve CR or PR on vismodegib as the best response have a better prognosis. This observation underlines the important position of vismodegib in the therapeutic landscape for BCC treatment and its positive impact on the duration of life. It is worth mentioning that quality of life data from the STEVIE trial showed that treatment with vismodegib was associated with improvement in the emotional domain in all subgroups at all time points.[15]

Despite the high clinical activity, toxicity is a crucial issue that can lead even to treatment discontinuation.[9–15,21] The majority of patients experienced at least one treatment-emergent AE (TEAE), similar to other trials in BCC.[9–15,21] In our study, the

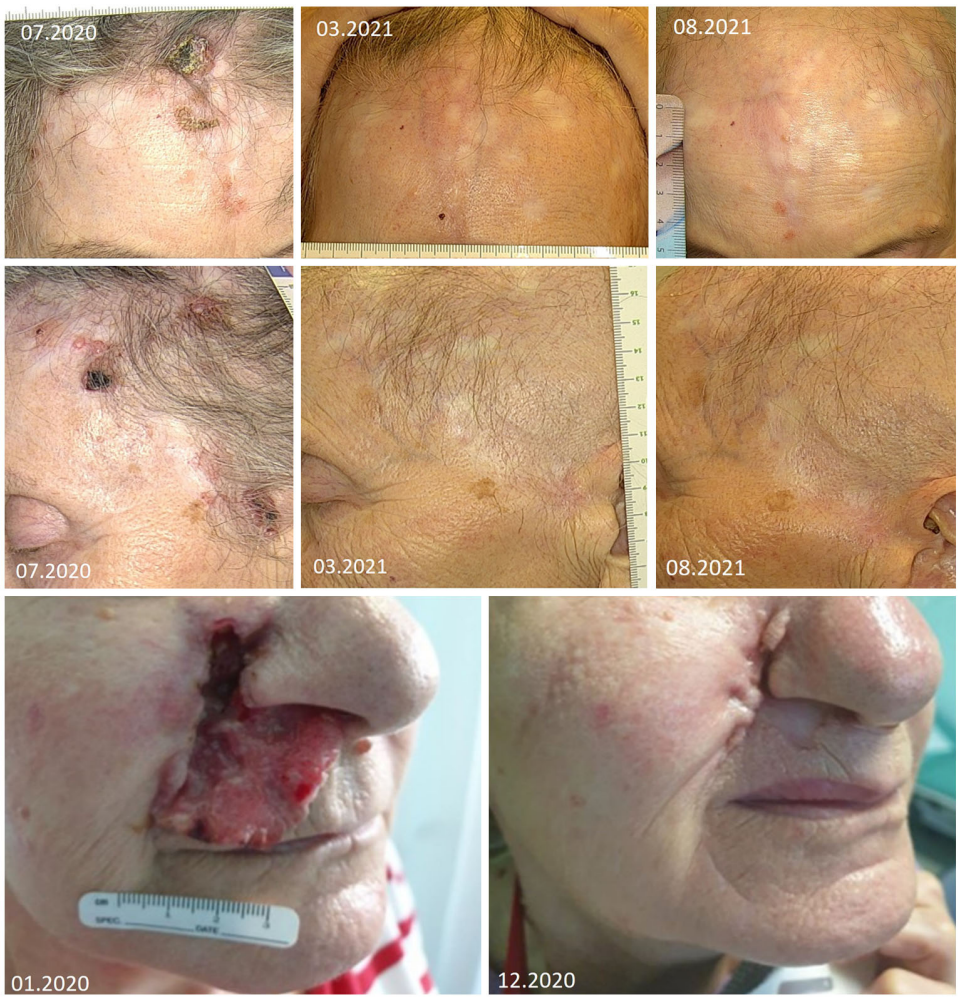

Figure 5 Response in two patients with laBCC after 12 months of therapy with vismodegib.

general toxicity profile was consistent with those reported in ERIVANCE and STEVIE studies.[10–15] The safety analysis revealed fewer AEs reported by the patients treated vismodegib in our study (83.3%) in comparison to the results of ERIVANCE (100%) and STEVIE (98%) studies, with less frequent alopecia and muscle spasms and more frequent decreased appetite.[10–15] Compared to the clinical trials, the frequency and severity of the weight loss, diarrhoea and fatigue, reported by the patients in our study was low.[10–15,21] As mentioned before, the retrospective nature of our study could impact on patients' reporting of AE symptoms (as most were subjective) and under-reporting in the medical records. Lower incidence of some AEs could result from strict patient selection or better side effects management.[21] It is important to note that during therapy with vismodegib AEs should be taken into account, although these are usually mild. Notably in our cohort, only two patients discontinued therapy due to AEs. This is a significantly lower number than in the ERIVANCE study, where 21.2% discontinued treatment due to AEs and 26% due to patient decision.[10–12] None of our patients developed squamous cell cancer during therapy with vismodegib although it is described in the literature.[23,24]

Our study included nine patients with Gorlin-Goltz syndrome. In our study, three patients were treated for less than 12 months and nine patients for at least 12 months. The median PFS for patients with this syndrome was 64 months, and median OS was not reached. In the ERIVANCE study, the ORR assessed by investigators in patients with GGS with laBCC was 81% (95% CI: 58–95%) and in patients without GGS 50% (95% CI: 34–66%).[10–12,25] In the EAS the best ORR was 33% (95% CI: 10–65%) in patients with GGS.[4,5,25]

Table 6 Summary of safety report during vismodegib treatment in this study

	ITT (*N* = 108) *N* (%)
Any AE	90 (83.3)
>1 AE/patient	52 (48.1)
Muscle spasms	66 (61.6)
Alopecia	52 (48.1)
Decreased appetite	36 (33.3)
Dysguesia	29 (26.9)
Weight loss	13 (12.0)
Nausea	9 (8.3)
Fatigue	6 (5.6)
Other	11 (10.2)
Diarrhea	3 (2.8)
Myalgia	2 (1.8)
Artralgia	1 (0.9)
Constipation	1 (0.9)
Increased AST/ALT	1 (0.9)
Stroke	1 (0.9)
SAE	5 (5.6)

AE, adverse event; SAE, serious adverse event.

A significant limitation to vismodegib treatment is the development of resistance by BCC, limiting the duration of response.[2,9,25–27] The secondary resistance is observed in about 20% of responders.[25–27] In our study, over half of the patients discontinued vismodegib due to disease progression, partially probably due to secondary resistance. BCC belongs to the neoplasms with the highest mutational burden. This indicates its potential sensitivity to immunotherapy.[27–30] The preliminary research results on immunotherapy in patients with BCC, including patients with PD during or after Hh inhibitors, are promising. Cemiplimab, the anti-PD1 antibody, has been assessed in patients with laBCC and mBCC in the phase II study (NCT03132636).[31] The preliminary results from the laBCC cohort (n = 84) showed an ORR of 31% (5 CR and 21 PR). Median DOR, PFS and OS were not reached, while the estimated PFS was 19 months.[31] Based on this data, cemiplimab has been approved by the FDA in February 2021. Also, some activity was shown for pembrolizumab, in a small investigator-initiated study.[29]

The data summarized in this manuscript have some limitations. The main limitations of this study include its retrospective character. Moreover, the study population is to some extent different than in pivotal clinical trials, primarily due to differences in eligibility criteria in clinical trials and drug programmes in Poland. Despite that, this study provides valuable data concerning the clinical management of locally advanced and metastatic BCC and confirmed the safety and efficacy of BCC treatment with vismodegib in a real-world setting.

Acknowledgements

Each patient, at the beginning of treatment provided routine informed consent for the use of their treatment, photos and data processing ('The patients in this manuscript have given written informed consent to publication of their case details'). The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board/Ethics Committee of Military Institute of Medicine (#21/WIM/2021). We thank Roche Polska Sp. z o.o, for financial support under the agreement of 27/11/2020.

Table 7 The summary of vismodegib efficacy in BCC based on our study, the ERIVANCE, and the STEVIE studies results[2,4,5,7,10-15]

	Our study (ITT population); *n* (%)	ERIVANCE mBCC (long-term analysis); *n* (%)	ERIVANCE laBCC (long-term analysis); *n* (%)	STEVIE mBCC; *n* (%)	STEVIE laBCC; *n* (%)
n	108	33	63	84	1077
ORR, *n* (%)	73 (67.6)	16 (48.5)	38 (60.3)	31 (36.9)	738 (68.5)
CR, *n*	19	0	20	4	360
PR, *n*	54	16	18	27	378
SD, *n*	28	14	15	39	270
PD, *n*	7	2	6	9	21
PFS, median, months	30.55 months [24.8–36.3]	9.3 [7.4–16.6]	12.9 [10.2–28.0]	13.1 [12.0–17.7]	23,2 [21.4–26.0]
OS, median, [95% CI]	41.5 months [31.6–51.3]	33.4 [18.1–NE]	NE [NE]	NA	NA
1-year survival rate, %	86	78.7	93.2	NA	NA
2-year survival rate, %	73	62.3	85.5	NA	NA

CI, confidence interval; CR, complete response; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NA, no data available; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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