

Effectiveness, Safety and Utilization of Vismodegib for Locally Advanced Basal Cell Carcinoma Under Real-world Conditions: Non-interventional Cohort Study JONAS

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Most patients with advanced basal cell carcinomas (BCCs) may not benefit sufficiently from standard treatment comprising surgery and radiation. Vismodegib, an oral selective hedgehog pathway inhibitor, is approved for treatment of patients with locally advanced BCC inappropriate for surgery or radiotherapy, or for patients with symptomatic metastatic BCC. In order to enhance understanding of the effectiveness, safety and utilization of vismodegib in clinical practice in Germany, a non-interventional study, JONAS, was conducted. A total of 53 patients with locally advanced BCC who initiated treatment with vismodegib between 2016 and 2018 were included in the study, which was embedded in the German ADOReg skin cancer registry. Duration of response, the primary endpoint, was 12.4 months, progression-free survival 32.2 months and overall response rate 77.4%. Most adverse events were mild to moderate. Overall, results confirmed previous findings, demonstrating favourable responses and manageable safety of vismodegib in patients with locally advanced BCC in clinical practice.

Key words: locally advanced basal cell carcinoma; vismodegib; effectiveness; safety; non-interventional study; German ADO-Reg skin cancer registry.

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Basal cell carcinoma (BCC) is the most common form of skin cancer and the most predominant of all cancers worldwide (1). In Germany, the prevalence of BCC is estimated at 200 cases in 100,000 persons per year (2). While most BCCs can be treated with surgery, the condition can, in rare cases, progress to advanced BCC (aBCC), further classifiable as locally advanced BCC (laBCC) or the, even rarer, metastatic BCC (mBCC) (3). Although the mortality of BCC is generally low, it can cause, particularly in its advanced stage, significant

SIGNIFICANCE

This study of advanced cases of the most common type of skin cancer, basal cell carcinoma, observed the treatment of 53 patients in Germany. Since their disease had advanced to the point where surgery or radiation was no longer an option, their treatment consisted of the oral drug vismodegib, which is approved for these patients. The aim was to evaluate the effectiveness, safety and use of vismodegib in routine practice. The majority of patients (77.4%) responded well to vismodegib treatment and no new, unexpected safety concerns were found. Thereby, the study confirmed the effectiveness and safety of vismodegib in clinical practice.

disfigurement among the affected and negatively impact on quality of life. In addition, in settings where delay of diagnosis and treatment occur, giant and invasive BCCs may develop with limited treatment options for such patients who often have several co-morbidities (4–6).

The principal drivers in the pathogenesis of aBCC are genetic alterations in the hedgehog (Hh) signalling pathway, resulting in abnormal pathway activation and uncontrolled cellular proliferation (7, 8). Hedgehog pathway inhibition thus represents a key therapeutic approach in the treatment and control of BCC. Vismodegib is the first oral, small molecule inhibitor of the hedgehog signalling pathway, approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of adults with symptomatic mBCC or laBCC, for whom surgery or radiotherapy are not indicated (9–11). A key study validating the effectiveness of vismodegib was the pivotal phase II trial ERIVANCE, a single-arm, 2-cohort, multicentre study in patients with confirmed laBCC or mBCC. In this long-term study, 104 patients with measurable aBCC who received oral vismodegib were observed for 39 months after completion of accrual, and the durability of response, efficacy across patient subgroups, and manageable long-term safety of vismodegib were demonstrated (12). Another interventional study, namely the single-arm, open-label, multicentre phase II trial

STEVIE, favourably evaluated the safety and efficacy of vismodegib in patients with laBCC or mBCC (13). The study showed a safety profile of the drug consistent with that of previous reports, with investigator-assessed response rates depicting high levels of tumour control.

In the more recent non-interventional study (NIS) NIELS, the aim was to provide further data on vismodegib safety and effectiveness for the treatment of laBCC in daily practice in Germany (14). A total of 66 patients at 26 German centres were observed in this study over 3 years and the results supported a long-term manageable safety profile of vismodegib in clinical practice, with no new unexpected safety signals uncovered (14). The present NIS JONAS aims to complement the results of the NIS NIELS by providing further data on effectiveness, safety and utilization of vismodegib for the treatment of aBCC patients in clinical routine in Germany.

MATERIALS AND METHODS

Patients and study design

This study was an observational, prospective, longitudinal, multi-centre cohort study in Germany. The target population comprised adult patients (≥ 18 years) diagnosed with laBCC inappropriate for surgery or radiotherapy, and patients diagnosed with histologically confirmed mBCC. Additional inclusion criteria were non-participation in any other trial and inclusion in the pregnancy prevention programme, as determined by the medical regulatory body in Germany (BfArM). Patients were excluded for whom treatment with vismodegib was contraindicated according to the Summary of Product Characteristics (15) in effect at the time of treatment.

The study aimed to recruit approximately 50 patients with laBCC and approximately 3 patients with mBCC from around 30 skin tumour sites participating in the German Dermatologic Oncology Cooperative Group's registry (ADOREg). A total of 13 ADOReg sites treating and managing patients with laBCC and mBCC, participated in the study with an enrolment of 53 patients with laBCC and no patients with mBCC. Eligible patients who received at least a single dose of vismodegib in routine clinical practice between Q1 2016 and Q1 2018 were enrolled over 2 years in the study. Patients were followed until disease progression, death, or for a maximum of 3 years from their first dose, whichever occurred first. The start of the study was 21 March 2016 (first patient in) and end of study 18 March 2021 (last patient out).

The study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and the Guidelines for Good Pharmacoevidence Practices issued by the International Society for Pharmacoepidemiology. The study protocol was approved by the ethics committee of the medical faculty of the University Duisburg-Essen, Germany, on 6 January 2016 (reference 15-6598-BO). The study was registered under clinicaltrials.gov identifier NCT02781389.

Study endpoints

The primary endpoint of the study was the duration of response (DOR), defined as the duration from the first documented complete (CR) or partial response (PR) until disease progression or death, as determined by the treating physician. The secondary endpoints comprised the following:

- best overall response (BOR), defined as best response (CR, PR, stable disease (SD) or progressive disease (PD)) during vismodegib treatment;

- objective response rate (ORR), namely rate of patients with CR or PR;
- disease control rate (DCR), defined as rate of patients with CR, PR or SD;
- recurrence rate, defined as rate of patients who had a CR and later progressed;
- progression-free survival (PFS), defined as the time interval between the date of first treatment with vismodegib and date of PD or death, whichever occurred first;
- overall survival (OS), defined as the time from first treatment to death; and
- time to response (TtR), defined as time to first CR or PR.

The safety endpoints were the prevalence proportion for all adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, and AEs leading to death. The exploratory endpoints for laBCC patient were: (i) type of tumour response evaluation as determined by the physician (i.e. clinical assessment, histological assessment or imaging); and (ii) utilization/treatment modalities considering: (a) BCC therapy prior to and after vismodegib therapy, (b) treatment duration with vismodegib (with and without periods of interruption), (c) time to first interruption, including number and duration of treatment interruptions and (d) reason for treatment interruption and discontinuation.

Statistical analysis

Data were either registered directly as part of ADOReg routinely collected data (in the ADOReg eCRF), or in the specific NIS JONAS eCRF built for the cohort study to collect additional data needed for this study. Individual patient data from the ADOReg database was sourced into the study database. Missing data were not imputed for this study. AEs and their severity were reported according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; v4.03).

The secondary endpoints BOR, ORR, recurrence rate, PFS and OS were analysed for patients of the Full Analysis Set (FAS) that comprised all patients who fulfilled the inclusion and exclusion criteria. The primary endpoint, DOR, and secondary endpoint, TtR, were analysed for those patients of the FAS whose confirmed best response was CR or PR. Safety endpoints were analysed for the Safety Analysis Set (SAF) that comprised all patients who received at least 1 vismodegib treatment.

Statistical analysis was descriptive and continuous variables described were means and standard deviations, as well as medians and interquartile ranges, minimum and maximum. For a description of categorical variables, frequencies and percentages were employed and 2-sided 95% confidence intervals (95% CIs) where appropriate. Kaplan–Meier survival estimates and curves were generated for time to event analyses. All analyses were conducted using SAS version 9.4.

RESULTS

Baseline characteristics

Overall, 53 patients with laBCC were enrolled and observed at 13 sites between March 2016 and March 2021. The study originally aimed to include both patients with laBCC and those with mBCC in 2 separate analysis populations; however, no patients with mBCC were recruited and analysis was carried out solely for the 53 patients with laBCC representing both the FAS and the SAF. No enrolled patients were excluded from these sets. The median study duration per patient was 22 months (range

9–34). Demographic and clinical characteristics of the study population are summarized in **Table I**.

Effectiveness results

BOR was CR in 18 (34.0%), PR in 23 (43.4%), and SD in 7 (13.2%) patients (**Table II**). Accordingly, the ORR was 77.4% (95% CI 63.8%; 87.7%) and the DCR was 90.6% (95% CI 79.3%; 96.9%). The DOR, i.e. the primary effectiveness endpoint, was evaluated based on the 41 patients for whom the objective response (CR or PR) was observed. The median DOR was 12.4 months (95% CI 8.3; 27.3) (Table II; Fig. S1a).

The recurrence rate 24 months after CR was 38.9% (7/18; 95% CI 17.3%; 64.3%) and did not change at later visits (Table II). The median PFS was 32.2 months (95% CI 16.8; 34.6) (Table II; Fig. S1b), median OS was not reached (Fig. S1c) and median TtR was 1.7 months (95% CI 1.0; 2.3) (Table II; Fig. S1d).

Table I. Baseline demographic and clinical data

| Characteristics | FAS (N = 53) |
|--|--------------|
| Sex, n (%) | |
| Men | 31 (58.5) |
| Women | 22 (41.5) |
| Age, years, mean (SD) | 74 (15.41) |
| Median (range) | 78 (31–98) |
| Age categories, n (%) | |
| <45 years | 4 (7.5) |
| 45–64 years | 10 (18.9) |
| 65–84 years | 26 (49.1) |
| ≥ 85 years | 13 (24.5) |
| BMI, kg/m ² , n (missing) | 35 (18) |
| Mean (SD) | 26.3 (4.28) |
| Median (range) | 26 (19–38) |
| ECOG PS, n (%) | |
| Missing | 9 (17.0) |
| 0 | 20 (37.7) |
| 1 | 19 (35.8) |
| 2 | 2 (3.8) |
| 3 | 1 (1.9) |
| 4 | 2 (3.8) |
| 5 | 0 (0) |
| Diagnosis, n (%) | |
| laBCC | 53 (100) |
| mBCC | 0 (0) |
| Assessment diagnosis (laBCC, mBCC), n (%) | |
| Histologically confirmed | 46 (86.8) |
| Not histologically confirmed | 7 (13.2) |
| Gorlin-Goltz syndrome, n (%) | |
| Yes | 6 (11.3) |
| No | 47 (88.7) |
| Treatment decision for vismodegib ^a , n (%) | |
| Dermato-oncologist | 45 (84.9) |
| Dermatologist | 44 (83.0) |
| Tumour board | 41 (77.4) |
| Radiotherapist | 28 (52.8) |
| Surgeon | 28 (52.8) |
| Plastic surgeon | 14 (26.4) |
| ENT specialist | 11 (20.8) |
| Ophthalmologist | 8 (15.1) |
| Other | 17 (32.1) |

^aSeveral answers possible.

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; ENT: ear, nose and throat; FAS: full analysis set; laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma; PS: performance status; SD: standard deviation.

Table II. Effectiveness results

| Effectiveness variable | FAS (n = 53) | 95% CI |
|--|--------------|--------------|
| BOR, n (%) | | |
| CR | 18 (34.0) | 21.5; 48.3 |
| PR | 23 (43.4) | 29.8; 57.7 |
| SD | 7 (13.2) | 5.5; 25.3 |
| PD | 1 (1.9) | 0.0; 10.1 |
| Missing | 4 (7.5) | 2.1; 18.2 |
| ORR, n (%) | 41 (77.4) | 63.8; 87.7 |
| DCR, n (%) | 48 (90.6) | 79.3; 96.9 |
| Median DOR, months | 12.4 | (8.3; 27.3) |
| Recurrence rate at observation visits after first record of CR, n/N–rate | | |
| 6 months | 1/18–5.6% | 0.1%; 27.3% |
| 12 months | 5/18–27.8% | 9.7%; 53.5% |
| 18 months | 6/18–33.3% | 13.3%; 59.0% |
| 24 months ^a | 7/18–38.9% | 17.3%; 64.3% |
| Median PFS, months | 32.2 | (16.8; 34.6) |
| Median TtR, months | 1.7 | (1.0; 2.3) |

^aNo further recurrences recorded in patients with complete response, i.e. recurrence rate did not change after 24 months post first record of CR.

BOR: best overall response; CI: confidence interval; CR: complete response; DCR: disease control rate; DOR: duration of response; FAS: full analysis set; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease; TtR: time to response.

Safety results

A total of 169 AEs in 37 (69.8%) patients were documented (**Table III**). The majority of AEs were mild (grade 1) to moderate (grade 2) in severity. The most frequently reported AEs of interest were “dysgeusia or ageusia”, followed by “muscle cramps” and “alopecia” (Table III). The most frequently reported other AE (i.e. not AE of interest) was “anorexia” (Table III).

Table III. Overview of adverse events

| Type of AE | Safety analysis set (N = 53) | | | |
|--|------------------------------|-------------|--|-------------|
| | Overall | | Related to vismodegib treatment ^a | |
| | Patients n (%) | Events n | Patients n (%) | Events n |
| Any AE | 37 (69.8) | 169 | 24 (45.3) | 86 |
| Grade 1 | 30 (56.6) | 104 | 20 (37.7) | 66 |
| Grade 2 | 22 (41.5) | 42 | 12 (22.6) | 17 |
| Grade 3 | 11 (20.8) | 18 | 3 (5.7) | 3 |
| Grade 4 | 2 (3.8) | 2 | 0 (0.0) | 0 |
| Grade 5 ^b | 3 (5.7) | 3 | 0 (0.0) | 0 |
| Frequent AEs of interest ^c (events reported for ≥10% of patients) | | | | |
| Dysgeusia or ageusia | 19 (35.8) | 22 | 13 (24.5) | 14 |
| Muscle cramps | 14 (26.4) | 18 | 5 (9.4) | 6 |
| Alopecia | 11 (20.8) | 11 | 10 (18.9) | 10 |
| Fatigue (≥grade 2) | 8 (15.1) | 8 | 7 (13.2) | 7 |
| Diarrhoea | 6 (11.3) | 7 | 3 (5.7) | 4 |
| Frequent any other AEs (events reported for ≥10% of patients) | | | | |
| Anorexia | 7 (13.2) | 7 | 5 (9.4) | 5 |
| SAEs | 9 (17.0) | 11 | 1 (1.9) | 1 |
| AEs resulting in treatment discontinuation | 13 (24.5) | 24 | 11 (20.8) | 21 |
| AEs leading to death | 2 (3.8) | 2 | 0 (0) | 0 |

^aAdverse events were considered related to vismodegib treatment if the relationship was evaluated as “possible”, “improbable”, “probable”, “yes” (i.e. related) by the treating physician. ^bSeverity for 1 serious adverse event (SAE) was reported as Grade 5, although the outcome was non-fatal. ^cAccording to the protocol, AEs of interest include muscle spasms, muscle cramps, arthralgia, alopecia (defined as hair loss anywhere on the body), dysgeusia or ageusia, taste alterations/disturbance, weight loss (unintentional), fatigue (grade 2 or higher), gastrointestinal events (grade 2 or higher), nausea, vomiting, constipation, diarrhoea, abdominal pain, elevated liver enzymes, cardiovascular (arterial/venous), stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism, congestive heart failure, amenorrhoea, women of child-bearing potential who report still menstruating at time of enrolment (definition from CTCAE v4.03), development of squamous cell carcinoma(s).

Eleven AEs in 9 (17.0%) patients were serious (Table III). Overall, 24 AEs in 13 (24.5%) patients resulted in discontinuation of treatment with vismodegib. Two AE ("death", system organ class "undefined") in 2 (3.8%) patients were fatal. Both patients with fatal AEs belonged in the age category ≥ 85 years and had discontinued vismodegib before the fatal event due to administrative reasons and increasing loss of appetite, respectively.

In total, 86 AEs in 24 (45.3%) patients were related to vismodegib, of which 1 AE was serious ("fracture", system organ class "injury, poisoning and procedural complications") and 21 AEs in 11 (20.8%) patients led to treatment discontinuation (Table III). The 2 fatal events were judged to be unrelated to vismodegib.

Exploratory results

Results on the type of tumour response assessment and on treatment utilization are summarized in Table SI. Clinical assessments were the most common type of tumour response evaluation. Thirty-five patients had a documented therapy before vismodegib. The majority of these patients had surgery alone. Twenty-four patients had a documented therapy after vismodegib (Table SI).

The median treatment duration was 6 months (range 0–56) both with and without treatment interruptions. The most frequent reasons cited for treatment interruption, apart from other than the predefined reasons, were patient's request and toxicity. The most cited reason for treatment discontinuation, apart from other than the predefined reasons, was PD, followed by patient's request and toxicity (Table SI).

DISCUSSION

The aim of this observational study was to enhance understanding of effectiveness, safety and utilization of vismodegib for the treatment of patients with aBCC in routine clinical practice in Germany. Despite limitations inherent in comparing clinical studies, analysis of similarly defined variables allows to put the results of the present NIS JONAS into context with results of the phase II trial ERIVANCE (primarily long-term final analysis in the laBCC cohort) (12, 16), the phase II trial STEVIE (laBCC cohort) (13) and the NIS NIELS (14). Comparability of those endpoints that are based on tumour response between the studies is limited by the fact that the assessment of tumour response was specifically defined for each study. In both the NIS JONAS and the NIS NIELS, tumour response was assessed by the physicians according to their routine practice and the method used was an exploratory variable. The results show that clinical evaluation is by far the most frequently used method in clinical practice compared with imaging and histological assessment.

DOR, the primary endpoint in this study was, with a median of 12.4 months, considerably shorter than the median DOR in the long-term ERIVANCE study of 26.2 months and the STEVIE study of 23.0 months. The NIS NIELS showed a more similar median DOR of 15.9 months.

Regarding secondary objectives, the proportion of patients with PR as BOR was higher in this study (43.4%) compared with the STEVIE study (35.1%) and the NIS NIELS (36.4%). Remarkably, SD was lower in this study (13.2%) compared with STEVIE (25.1%), while the PD in the current study was also lower than in NIS NIELS (1.9% vs. 4.5%). Overall, the ORR of 77.4% in this study was higher than in the ERIVANCE study at 60.3%, and the STEVIE study at 68.5%, but similar to the NIS NIELS at 74.2%.

The PFS was the longest in this study at a median of 32.2 months (95% CI 16.8; 34.6), compared with the ERIVANCE at 12.9 months (95% CI 10.2; 28.0) (12), the STEVIE at 23.2 months (95% CI 21.4; 26.0) and the NIS NIELS at 19.1 months (95% CI 13.8; 26.5). The median OS could not be estimated in any of the studies, considering the higher survival rate in this cohort of study patients. Although the CR was similar, recurrence rates were higher at the different time-points after 6/12/18/24 months in the NIS NIELS than in this study: 12.0/32.0/48.0/52.0% in the NIS NIELS compared with 5.6/27.8/33.3/38.9% in the NIS JONAS. This underscores the natural inherent differences and heterogeneity in any given study population, leading to divergent, unpredictable outcomes in disease progression. Overall, death rates were lower in this study (3.8%) compared with the NIS NIELS (15.2%), ERIVANCE (20.6% at 39 months after completion of accrual) and STEVIE (8.2%).

The safety profile of vismodegib remained consistent with that previously reported. The most common AEs were muscle spasm, dysgeusia, and alopecia, classical effects associated with on-target inhibition of the hedgehog signalling pathway (12, 17). As both the NIS JONAS and the NIS NIELS were conducted in Germany, with comparable data presentation, the safety discussion compares just these 2 studies. In contrast to the NIS NIELS where almost all patients (95.5%) presented with AEs, the incidence was considerably lower in this study (69.8%). The majority of AEs were of a mild to moderate nature (grade 1–grade 2) in both studies. Notably, only in the NIS JONAS was an unexpectedly large proportion of the most frequently observed AEs of special interest judged by the physicians to be unrelated to vismodegib ("dysgeusia or ageusia", "muscle cramps"; Table III). The physicians' reasons for the assessment were not documented. There were more SAEs in the NIS NIELS than in the current study; most SAEs were unrelated to vismodegib. Strategies to manage AEs during vismodegib treatment therefore remain a high priority in order to

enable patients to remain on treatment and consequently receiving its full benefit (12).

Sonidegib is another hedgehog pathway inhibitor approved for the treatment of laBCC, following promising results of the BOLT pivotal study (17, 18). Similarities in findings were observed between the BOLT trial and the current study: ORR of 71.2% in the BOLT study compared with 77.4% in this study, median DOR of 15.7 months compared with 12.4 months in this study. Thus, hedgehog pathway inhibition appears to be a feasible and effective treatment option for aBCC.

As with any non-interventional study, the NIS JONAS had some limitations. To minimize selection bias, the dermatologists and sites participating in the ADOReg were selected as representing most of the large as well as small dermatology departments in Germany. In addition, eligibility criteria were selected to be as broad as possible for this study population. Because of the low prevalence of aBCC (19), patient recruitment was nevertheless difficult. The study originally aimed at assessing treatment effectiveness of vismodegib for management of laBCC and mBCC. However, as no mBCC patients were enrolled, the study focussed only on the laBCC cohort. Moreover, there is a risk of under-reporting of AEs, and this may be only partially mitigated by solicited collection methods used in this study.

In conclusion, the results of the NIS JONAS harmonize well with previous studies, especially the NIS NIELS, demonstrating favourable responses and safety of vismodegib in patients with laBCC in clinical practice.

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