Dermatology Practical & Conceptual

A Non-Interventional Study on Vismodegib for Basal Cell Carcinoma in Swedish Patients

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ABSTRACT

Introduction: Real-life data on vismodegib in advanced basal cell carcinoma (aBCC) are limited. Optimal treatment duration is left to the discretion of the physician.

Objectives: To assess the effectiveness, safety and treatment pattern for vismodegib in aBCC in clinical practice.

Methods: In this multicenter, non-interventional, prospective study, 49 Swedish patients planned for vismodegib treatment were included. The treatment pattern observed was treatment until remission, allowing unlimited discontinuations/pauses.

Results: The majority of patients (93.8%), discontinued at least once during the study. Compared to earlier studies there was a decrease of more than 2 months with actual drug intake, reducing the patients burden and costs, at the same time as a high number of responses were seen (87.8%). Median progression-free-survival was 16.7 months, and 90% of the patients were alive at 13.3 months. Ten patients were re-challenged with vismodegib at recurrence or progression, resulting in five partial remissions and three complete remissions.

Conclusions: Clinical response rates with vismodegib for aBCC were comparable to those of similar trials despite a shorter and more intermittent treatment duration. The majority of re-challenges lead to partial or complete remissions.

Introduction

Basal cell carcinoma (BCC) is the most common human cancer. In Sweden, the number of histopathologically verified BCC cases have increased 10-fold during the last 30 years. In 2019, the number of patients reported to the Swedish Cancer Registry were >61 000, compared to 36 500 in 2008 [1].

The most common reason for BCC is chronic or intermittent exposure of UV-radiation, where the disease development is driven by an abnormal activation of the Hedgehog signaling pathway [2-6]. The majority of BCCs occur sporadically, but a rare autosomal dominant inherited condition, Gorlin syndrome, also exists [7-9]. Vismodegib (Erivedge®, Hoffmann-La Roche Ltd, Basel, Switzerland) is a first-in-class, oral small molecule inhibitor of the Hedgehog signaling pathway, developed to treat hedgehog mutated tumors. The European approval of vismodegib was based on the pivotal study ERIVANCE, an international, phase-2, open-label, non-comparative clinical trial that showed high efficacy and acceptable tolerability in patients with metastatic or locally advanced BCC with or without Gorlin syndrome [10, 11]. The results were confirmed in a larger multicenter safety study, STEVIE [12]. Both trials included continuous treatment with vismodegib 150 mg once daily, until disease progression or intolerable toxicity. Thirty-one percent of the patients discontinued treatment due to toxicity, although treatment interruptions/pauses up to 4-8 weeks were allowed. To overcome the toxicity with maintained efficacy, the dosing regimen has been further evaluated in several trials, as intermittent dosing, or reduced dosing [13-16]. However, there is no established guideline for optimal treatment duration with vismodegib.

At the time of initiation of this non-interventional study (NIS), data on treatment in a real-life setting was lacking in Sweden as well as world-wide. Implementing a systematic data collection was encouraged by the necessity to increase knowledge of current treatment patterns, effectiveness and safety. Since then, three similar European studies with data collected both retrospectively and prospectively have been published: one from Greece with 67 patients and two from Germany with 66 and 53 patients, respectively, have been published [17-19]. The current study intends to add more data to the growing collection of evidence on real-life treatment with vismodegib.

Methods

Study Population, Cohorts and Data Collection

This study was a non-interventional, prospective cohort study in adult patients with aBCC. All patients were planned for vismodegib treatment within normal routine practice according to the current product label. Following non-interventional study guidelines, study assessments and timing of visits were not mandatory, but performed according to routine care at each participating clinic (www.encepp.eu 2011). Guidelines for Good Pharmaco-epidemiological Practice (GPP) were followed and approval by the Swedish Ethical Review Authority was obtained prior to study start in December 2014 (www.pharmacoepi.org). An overview of the study details is published on www.clinicaltrials.gov, NCT 02371967.

The study enrolled 50 patients at four university hospitals in Sweden between April 2015 and September 2017, with a follow-up period of 3 years. The trial sites were two dermatology clinics (Skåne University Hospital and Sahlgrenska University Hospital) and two oncology clinics (Karolinska University Hospital and Norrland University Hospital).

Patients included were ≥18 years old, with a diagnosed aBCC, defined as metastatic or locally advanced (where other therapy such as surgery or radiotherapy were not an option), or Gorlin syndrome requiring systemic treatment and planned for treatment with vismodegib. A signed informed consent for collection of data was obtained from all patients before enrolment. All patients were divided into three cohorts: cohort 1 included patients with aBCC without Gorlin syndrome and not previously exposed to a hedgehog pathway inhibitor (HPI), cohort 2 included patients with aBCC without Gorlin syndrome that previously had been exposed to an HPI and cohort 3 included patients with Gorlin syndrome independent of previous exposure to an HPI. Patients previously included in other clinical trials within 90 days were excluded, with exceptions for patients in cohort 2.

The aim of the study was to assess effectiveness, safety and treatment patterns of vismodegib treatment in a real-life setting. Clinical outcomes included: clinical response, time to response, duration of response, recurrence rate, progression-free survival and overall survival. Safety objectives included: incidence, severity, and relationship of adverse and serious adverse events (SAEs) including pregnancies, and adverse events leading to treatment interruption or

discontinuation. Toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4. Adverse events of special interest (AESI) included: muscle spasms, alopecia, dysgeusia/ageusia, weight loss, fatigue of grade ≥2, amenorrhea, gastrointestinal events grade ≥2, cardiovascular events and secondary malignancies.

Patient data were collected from the patient's medical records into an electronic case report form (CRF) (Viedoc™, Viedoc Technologies, Uppsala, Sweden) and data quality was checked by on-site and remote monitoring. Analysis of data was done after a clean file report and database lock.

Statistical Analysis

The statistical analysis was done according to the ICH E9 guideline for Statistical Principles of Clinical Trials using SAS® (version 9.4 or higher). The intention-to-treat (ITT) population used for the effectiveness analysis was defined as all patients enrolled in the study. The safety population was defined as all patients who received at least one dose of vismodegib during the study. MedDRA terminology was used for adverse events and NCI CTCAE version 4 was used for toxicity grading. Tumor assessments were done by radiological assessment using RECIST v 1.1. and/or by clinical assessment.

The analysis of the study was exploratory and descriptive methods were used, presenting data by cohort and in total. No pre-specified hypotheses were defined, the sample size of 50 patients was regarded as sufficient to characterize the treatment pattern considering the rare indication of aBCC. Continuous data were summarized as the number of subjects with evaluable observations and missing observations, arithmetic mean and standard deviation, median with first and third quartiles, minimum and maximum. Categorical data were presented using frequency and percentage. Confidence intervals were 2-sided with a 95% confidence interval.

Drug exposure was summarized with number and percentage of patients for the total exposure, maximum treatment duration, including breakdowns for treatment pauses and dose modifications. More than one treatment discontinuation or dose modification could be reported for each patient.

Results

In total, 50 patients were enrolled. One patient was found non-eligible prior to drug intake and excluded from the study. The remaining 49 patients comprised the ITT population. One of these patients withdrew consent prior to first administration of vismodegib. Thus, the remaining 48 patients constituted the safety population.

In total, 40 patients were diagnosed with aBCC without Gorlin syndrome. The majority of these, 37 patients, were not previously exposed to an HPI and allocated to cohort 1. Thus, three patients were allocated to cohort 2. Nine patients with Gorlin syndrome were allocated to cohort 3 independent of previous exposure to an HPI. Baseline patient characteristics can be found in Table 1. One patient of childbearing potential was included and followed with monthly pregnancy tests up to 1 year after treatment completion. All tests were negative.

All patients had an ongoing locally advanced or metastatic BCC or Gorlin syndrome at enrollment, and two patients had recurrent disease following previous treatment. Six patients (12.2%) had other prior cancer history (fibrosarcoma, lymphoma, melanoma, nasopharyngeal cancer, prostate cancer and squamous cell carcinoma). The most frequent non-cancer condition was hypertension. Six patients (12.2%) were reported to have received vismodegib previously, all patients in cohort 2 and three patients in cohort 3. At baseline, the extent of the disease was clinically assessed in 34 patients whereas 14 patients also required radiological assessment.

More than half of the study population, 28 patients (57.1%) completed the study with a 3-year follow-up period. The remaining study population (21 patients, 42.9%) withdrew prematurely from the study. The most common reasons were death (not related to treatment) or progressive disease.

Treatment discontinuations and pauses were frequent and reported at least once by 45 patients (93.8%) during the study. The most common reasons were complete remissions (22 patients) and adverse events (14 patients). Median duration of exposure (including days off treatment) was 5.7 months (range 1-35.9 months) and 5.2 months (range 1-35.5 months) excluding days off treatment (Table 2). The overall treatment pattern with number of days of treatment and pauses from treatment per patient showed high variability (Table 3).

Of the 49 included patients, 43 (87.8%) achieved a clinical response (95% CI; 75.2-95.4%). Clinical response was observed in 34 patients (91.9%) in cohort 1, two patients (66.7%) in cohort 2 and seven patients (77.8%) in cohort 3. Approximately half of the responses were complete remissions as best response. At 2 months of treatment (60 days), approximately half of the study population had achieved a clinical response, and at 3.3 months (100 days), 80% of the patients had achieved a clinical response. Median duration of response was approximately 14.3 months (430 days).

Recurrence during the study occurred in 14 patients (28.6%), 11 of these patients were in cohort 1 and three patients were in cohort 3. The median time to recurrence was

Table 1. Baseline characteristics.

	Cohort 1 (N=37)	Cohort 2 (N=3)	Cohort 3 (N=9)	Total (N=49)
Age, years, mean (SD)	78 (11)	66 (20)	56 (11)	73 (14)
Age, years, min-max	50-97	46-85	43-74	43-97
Female, n (%)	16 (43)	0	2 (22)	18 (37)
Male, n (%)	21 (57)	3 (100)	7 (78)	31 (63)
Height, mean (SD), cm	171 (11)	179 (8)	184 (9)	173 (11)
Weight, mean (SD), kg	76 (19)	91 (11)	96 (25)	80 (21)
ECOG performance status, n (%)				
ECOG 0-1	31 (84)	3 (100)	8 (89)	42 (86)
ECOG 2	1 (3)	0	1 (11)	2 (4)
ECOG 3	4 (11)	0	0	4 (8)
ECOG 4	1 (3)	0	0	1 (2)
BCC assessment at time of diagnose, n (%)				
Clinical, histopathology	0	0	2 (22)	2 (4)
Clinical	2 (5)	0	2 (22)	4 (8)
Histopathology	23 (62)	1 (33)	0	24 (49)
Unknown	10 (27)	2 (67)	5 (56)	17 (35)
Missing data	2 (5)	0	0	2 (4)
Previous medical treatments, n (%)[a]				
Imiquimod	1 (3)	0	0	1 (2)
Vismodegib	0	3 (100)	3 (33)	4
Previous surgical procedures, n (%)[b]				
Surgery	14 (37.8)	0	1 (11.1)	15 (30.6)
Cryotherapy	2 (5.4)	0	0	2 (4.1)
Cryosurgery	1 (2.7)	0	0	1 (2.0)
Cardiac pacemaker insertion	0	1 (33.3)	0	1 (2.0)
Previous radiotherapy and photodynamic therapy n (%)[b]				
Radiotherapy	5 (13.5)	0	0	5 (10.2)
Photodynamic therapy	1 (2.7)	0	0	1 (2.0)

[a]reflect at least 14 days prior to study start
[b]last 10 years prior to study start

approximately 20 months (600 days) and there was a 20% probability of an early recurrence at 6.7 months (200 days).

Ten patients were re-challenged due to progression after an initially achieved response. Eight reached new remissions, five with partial remissions and three with complete remissions. Both complete and partial responses were achieved. Two patients were even re-challenged twice with repeated partial remissions as response.

The median progression-free survival (PFS) was estimated to be 16.6 months (500 days). The 80% overall survival rate was 2.7 years and the 90% overall survival rate (OS) was 13 months. A median overall survival was not reached within the study period (Figure I).

There were 45 patients (93.8%) that experienced at least one adverse event, with a total of 194 events. Of these, 150 events (77.3%) were regarded to be at least possibly related to vismodegib treatment. Most adverse events were mild or moderate and commonly reported as muscle spasms, dysgeusia and alopecia. Severe adverse events were reported on 17 occasions, where three events (ageusia, dysgeusia and fatigue) were deemed as related to vismodegib treatment.

The frequencies of predefined AESIs can be found in Table 4.

A total of 19 SAEs were reported during the entire study period by 16 patients (33.3%). Of these, 11 SAEs had a fatal outcome. Causes of death included natural causes (3 patients), cardiac failure (2 patients), stroke, complications after brain surgery, gastrointestinal bleeding, metastatic disease and in two patients the cause was unknown. One patient died while on treatment due to natural causes and 10

Table 2. Disposition of patients, exposure of drug and efficacy.

	Cohort 1	Cohort 2	Cohort 3	Total
Patients enrolled	**n=37**	**n=3**	**n=9**	**n=49**
Completed the study, n (%)	20 (54.1)	2 (66.7)	6 (66.7)	28 (57.1)
Prematurely withdrawn from the study, n (%)	17 (45.9)	1 (33.3)	3 (33.3)	21 (42.9)
Patients treated	**n=37**	**n=3**	**n=8**	**n=48**
Discontinued treatment at least once during the study, n (%)	35 (94.6)	3 (100.0)	7 (87.5)	45 (93.8)
Reason of discontinuation from treatment, n (%)				
Complete remission	15 (42.9)	1 (33.3)	6 (85.7)	22 (48.9)
Adverse Event / Serious Adverse Event	10 (28.6)	1 (33.3)	3 (42.9)	14 (31.1)
Death	1 (2.9)	0	0	1 (2.2)
Progressive disease	3 (8.6)	0	0	3 (6.7)
Lack of efficacy	4 (11.4)	0	1 (14.3)	5 (11.1)
Physician decision	5 (14.3)	1 (33.3)	0	6 (13.3)
Other	4 (11.4)	0	5 (71.4)	9 (20)
Exposure of drug				
Treatment duration, (incl days off treatment), months				
Mean (SD)	11.7 (11.5)	12.5 (19.2)	16.2 (13.3)	12.4 (12.0)
Median (range)	5.8 (1-35.9)	1.4 (1.4-34.8)	15.2 (2.8-35.7)	5.7 (1-35.9)
Treatment duration (excl days off treatment), months				
Mean (SD)	8.1 (7.0)	11.1 (16.8)	8.8 (8.2)	8.4 (7.8)
Median (range)	5.6 (1-35.5)	1.4 (1.4-30.6)	4.1 (2.8-23.9)	5.2 (1-35.5)
Effectiveness	**n=37**	**n=3**	**n=9**	**n=49**
Clinical response (complete or partial remission), n (%)	34 (91.9)	2 (66.7)	7 (77.8)	43 (87.8)
95% CI	(78.1-98.3)	(9.4-99.2)	(40.0-97.2)	(75.2-95.4)
Recurrence during the study, n (%)	11 (29.7)	0	3 (33.3)	14 (28.6)
95% CI	(15.9-47.0)	(0.0-70.8)	(7.5-70.1)	(16.6-43.3)
Median time to response, all patients, months				2
Median duration of response, all patients, months				14.3
Median time to recurrence, all patients, months				20
Median progression-free survival, all patients, months				16.6
Median overall survival, all patients, months				Not reached

n, number of patients; SD, standard deviation.

Since this was an observational study, patients were taking treatment according to normal routine practice. Because of this, each patient could report more than one treatment discontinuation (i.e. a patient can discontinue and then restart treatment several times). The table summarizes the number of patients who discontinued at least once including each unique reason for discontinuation.

patients died during the follow-up period. None of the fatal events were assessed as related to vismodegib.

Ten patients (20.8%) withdrew treatment due to an adverse event (Table 4). The reasons were ageusia/dysgeusia, weight loss, asthenia, fatigue, muscle spasms/weakness, nausea, pruritus and back pain.

There were 12 adverse events reported by seven patients (14.6%) that resulted in an interruption or discontinuation of vismodegib. The reasons were gastrointestinal disorders, nausea, vomiting, diarrhoea, fatigue, dysgeusia, upper limb fracture, loss of effect and weight loss (Table 4).

Conclusions

The aim of the current study was to systematically collect data on effect, safety and treatment patterns of vismodegib in a real-world setting. The resulting study population correlates well in general to other studies on the use of

Table 3. Extent of exposure including duration of treatment and pauses from treatment.

	Cohort 1 n=37	Cohort 2 n=3	Cohort 3 n=8	Total n=48
Total duration of exposure in days				
n/nmiss	37/0	3/0	7/1	47/1
Mean (SD)	350.1 (344.0)	376.3 (577.4)	485.0 (399.8)	371.8 (361.0)
Median	173.0	43.0	456.0	173.0
Q1, Q3	85.0, 441,0	43.0, 1043.0	104.0, 840.0	85.0, 717.0
Min, Max	30, 1076	43, 1043	85, 1070	30, 1076
Total number of days on treatment				
Mean (SD)	241.9 (210.8)	334.3 (504.6)	262.6 (245.8)	250.9 (232.9)
Median	167	43	124	156
Q1, Q3	85.0, 361.0	43.0, 917.0	104.0, 497.0	85.0, 374.0
Min, Max	0, 716	43, 917	85, 717	30, 1066
Total number of days on pause from treatment				
Mean (SD)	108.1 (230.2)	42.0 (72.7)	222.4 (293.6)	120.9 (234.6)
Median	0.0	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 126.0	0.0, 573.0	0.0, 0.0
Min, Max	0, 716	0, 126	0, 652	0, 716

n/nmiss, number of subjects with evaluable/missing data; Q1, first quartile; Q3, third quartile; SD, standard deviation. The same patient could report more than one treatment discontinuation.

vismodegib for aBCC, including the pivotal study ERIVANCE [10, 11], the safety study STEVIE [12, 20] and the more recently published non-interventional studies from Germany [18, 19] and Greece [17]. In the current study, the group with Gorlin syndrome were markedly younger than the overall populations, as could be expected with the greater severity and earlier onset of disease for these patients [7, 8]. The predominance of men compared to women in the current study is similar to most studies [11-13, 17-19, 21] and the baseline comorbidity and concomitant treatments as could be expected with respect to the ages and the disease indication.

The obtained study data support previous knowledge of vismodegib as highly effective; the PFS and OS levels are in line with the pivotal ERIVANCE and STEVIE trials [18, 12] whereas the clinical response of 95.4% in this trial is high compared to other studies, where 50-77% clinical responders were observed [11, 13, 18, 19] and similar to the Greek study that reported 95.6% responders [17]. The variability in clinical response rate between studies is most likely due to differences in response evaluation methods. The current study pragmatically allowed for physician assessment to determine clinical response in order to reflect the real-world practice and thus a resulting higher response rate than when using strict radiologic criteria is to be expected.

Approximately half of the patients had reached a clinical response after 2 months (60 days), and 80% after 3.3 months (100 days) of treatment. This is a shorter time to response, compared to the median time of 5.5-6.7 months in the pivotal study [11] and comparable or slightly shorter than the median time to response of 2.7 months in the German real-world study [18]. Again, the differences between a controlled and a real-world setting is probably the main reason for the shorter time to response reported in the non-interventional studies. The results illustrate the relatively short time to a clinically relevant effect when used in everyday healthcare.

Interestingly, ten patients were re-challenged with vismodegib resulting in five partial remissions and three complete remissions. Two patients were even re-challenged twice with repeated remissions. These data are in line with the Greek study that reported responses after re-challenging in 8 patients [17].

Of the predefined AESIs, the frequencies of alopecia, fatigue, nausea and weight-loss were lower or much lower compared to those reported in the ERIVANCE and STEVIE studies. Other adverse events were as expected in frequency and most events were mild to moderate [11, 12]. Ten patients (20.8%) discontinued treatment due to adverse events, while seven patients (14.6%) interrupted or discontinued treatment but could remain on treatment regimen. Compared to previously reported trials, this is a low frequency. There were more SAEs reported in this study (33.3%) compared to the German studies that reported 22.7% and 17.0%, respectively. Nevertheless, the majority of the SAEs were not related to vismodegib in any of the studies [18, 19]. Of the

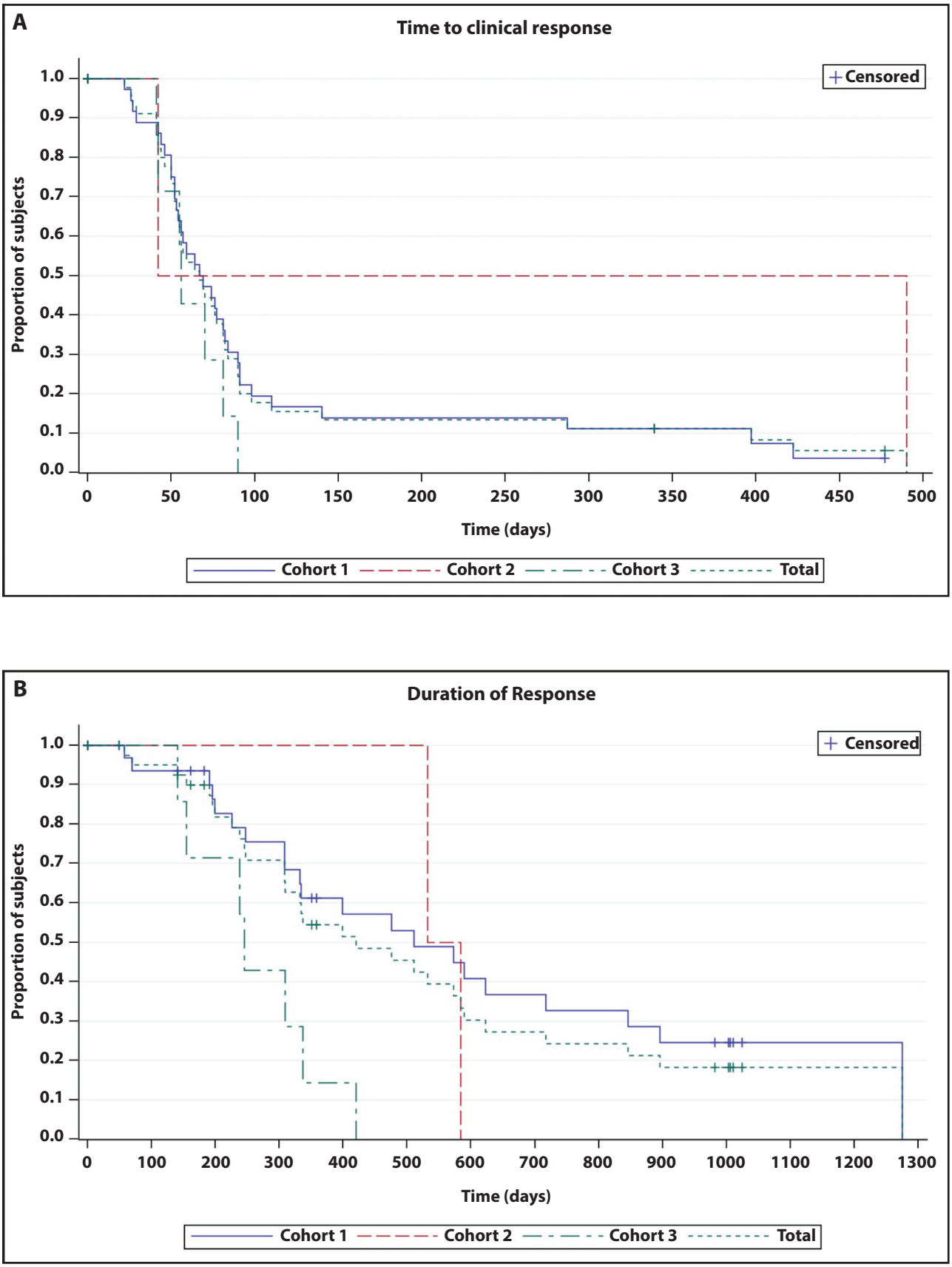

Figure 1. Kaplan-Meier plots of (A) time to clinical response, (B) duration of response and (C) time to recurrence on cohorts 1, 2, 3 and in total.

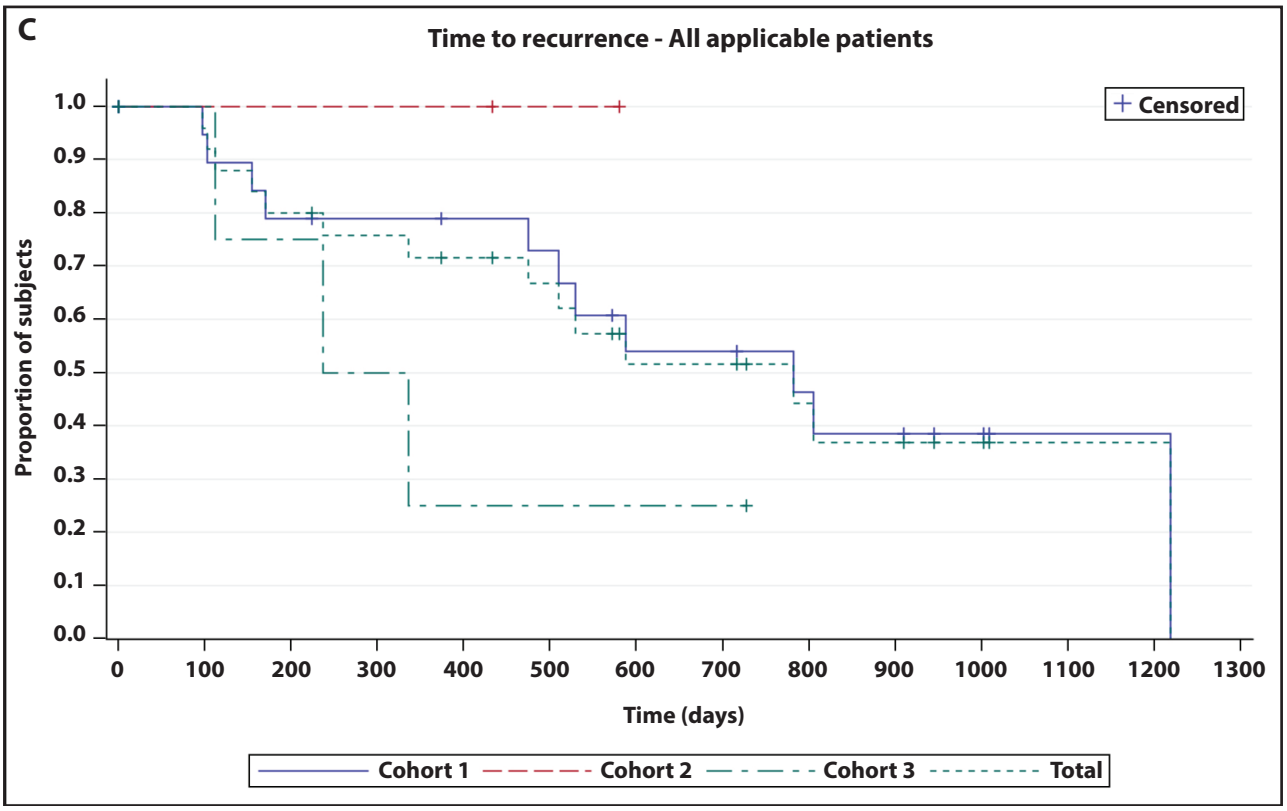

Figure 1. Kaplan-Meier plots of (A) time to clinical response, (B) duration of response and (C) time to recurrence on cohorts 1, 2, 3 and in total. (*Continued*)

Table 4. Adverse events, safety population.

	Cohort 1 (n=37)	Cohort 2 (n=3)	Cohort 3 (n=8)	Total (n=48)
Any adverse event, n (%)	35 (94.6)	3 (100.0)	7 (87.5)	45 (93.8)
Any adverse event of special interest, n (%)	28 (75.7)	1 (33.3)	7 (87.5)	36 (75.0)
Any serious adverse event, n (%)	13 (35.1)	1 (33.3)	2 (25.0)	16 (33.3)
SAEs with fatal outcome, n (%)	11 (29.7)	0	0	11 (22.9)
Adverse event leading to withdrawal of study treatment[b], n (%)	**8 (21.6)**	**0**	**2 (25.0)**	**10 (20.8)**
Number of events	**14**	**0**	**2**	**16**
Ageusia/dysgeusia	4 (21.6)	0	2 (25)	
Abnormal weight loss	2 (5.4)	0	0	
Asthenia	1 (2.7)	0	0	
Fatigue	2 (5.4)	0	0	
Muscular weakness	1 (2.7)	0	0	
Muscular spasm	3 (8.1)	0	0	
Nausea	1 (2.7)	0	0	
Pruritus	0	0	1 (12.5)	
Back pain	0	0	1 (12.5)	
Adverse events leading to interruption of study treatment, n	**5 (13.5)**	**1 (33.3)**	**1 (12.5)**	**7 (14.6)**
Number of adverse events leading to interruption of study treatment	**9**	**2**	**1**	**12**
Nausea	1 (2.7)	1 (33.3)	0	2 (4.2)

Table 4. Adverse events, safety population. *(Continued)*

	Cohort 1 (n=37)	Cohort 2 (n=3)	Cohort 3 (n=8)	Total (n=48)
Diarrhoea	1 (2.7)	0	0	1 (2.1)
Gastrointestinal disorder	1 (2.7)	0	0	1 (2.1)
Vomiting	1 (2.7)	0	0	1 (2.1)
Drug ineffective	2 (5.4)	0	0	2 (4.2)
Fatigue	0	1 (33.3)	0	1 (2.1)
Dysgeusia	2 (5.4)	0	0	2 (4.2)
Upper limb fracture	0	0	1 (12.5)	1 (2.1)
Abnormal loss of weight	1 (2.7)	0	0	1 (2.1)

n = number of subjects

[a] 10 of the fatal SAEs occurred during the follow-up period and 1 during the treatment phase. 3 fatal SAEs occurred during the follow-up study phase but were found after database lock and are included here.
[b] The same patient can report more than one event.

life-threatening or fatal events, none were judged to be related to vismodegib treatment.

In all, a non-interventional study design cannot be compared to the strength of a controlled clinical trial. The data collection follows the standard care at each study site and obviously varies between clinics. Treatment durations were not standardized but adjusted to each patient and frequent treatment pauses were allowed; all which might influence the response outcome. The patient demographics show some imbalances between the cohorts, but with exception of the younger age in cohort 3, these differences do not appear relevant. Comparison of the cohorts must be done with great caution, due to the big differences in number of patients between them. However, in general the collected data mirror the standard of care of the patient population at each clinic and reflect the real-life treatment of patients with aBCC, which was the purpose of the study.

To conclude, this study is the largest study performed in Sweden with aBCC patients treated with vismodegib and mirrors the routine clinical care of aBCC. Vismodegib treatment resulted in a high number of patients with a clinical response and PFS and OS in the same range as in other trials despite a shorter and more intermittent treatment duration. The close monitoring of patient safety, tolerability and adaptation of treatment, including re-challenge of treatment in some cases, may be a step towards optimizing the treatment schedule of aBCC patients.

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