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ARTICLE

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The initial rate of tumour response to vismodegib treatment, can predict a complete response outcome for periocular LA-BCC

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PURPOSE: To establish a model to predict treatment outcome of periocular locally advanced basal cell carcinoma (POLA BCC) based on initial response to treatment with vismodegib (Erivedge™), a sonic hedgehog inhibitor.
DESIGN: Subgroup analysis of data from the STEVIE study database.
METHODS: Analysis of medical history, treatment protocol, and treatment outcome of POLA BCC tumours in a STEVIE study population of 244 POLA BCC patients treated with ≥1 dose of vismodegib.
RESULTS: A predictive model for complete response (CR) was established based on the initial treatment response. A cutoff value of 20% reduction in tumour size at 3 months of treatment identified the patients with a high probability (82.76%) to achieve CR. A second cutoff value of 67.7% reduction in tumour size at 6 months of treatment improved the prediction to a 95.42% probability of a CR outcome.
CONCLUSIONS: A treatment model was constructed based on the prediction of a CR outcome and the initial response to vismodegib treatment at 3 and 6 months. The study result provide significant new insights can facilitate decision-making on treatment management according to tumour response in patients with POLA BCC.

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer worldwide [1]. It is more common than all other cancers combined, and its incidence is constantly on the rise [1, 2]. Periocular-BCC is diagnosed in 4.4–18% of all BCCs, accounting for approximately 90% of all malignant periocular tumours [3]. Surgical excision is considered the treatment of choice for most basic lesions. However, in some patients, the disease progresses to a more extensive locally-advanced BCC (LA-BCC). Approximately 20% of all LABCC are located in the periocular region. POLA BCC represents a stage in which the tumour is inoperable or curable surgery may require extensive removal of ocular adnexa, which can affect ocular function by several means [4, 5]. These include impairment of normal blinking, disruption of the ocular surface, and restriction in ocular motility or even loss of the eye and orbit (i.e. orbital exenteration). Preservation of vision should therefore be one of the main factors to consider when choosing between treatment options [2, 6]. In general, it represents a stage where the tumour is inoperable or where the curable surgery may require extensive removal of the ocular adnexa and therefore is associated with severe morbidity and even loss of the eye itself [7].

Vismodegib (Erivedge™), a first class Hedgehog pathway inhibitor (HHI), was approved by the FDA in 2012 for the treatment of LA BCC and metastatic BCC. Approximately 350 cases of POLA-BCC treated with vismodegib have since been reported, most taken from the STEVIE study, which is a single-arm, multicentre, open-label study involving 167 treatment sites in 36 countries [2, 8–10]. The POLA-BCC cases from the STEVIE study reported the outcome of vismodegib for periocular tumours, with a 67.2% overall response rate (28.7% complete response [CR] and 38.5% partial response [PR]) [9]. Vismodegib treatment is administered for very long periods of time, and side effects, which occur in 98% of patients, are the main reason for treatment discontinuation and treatment failure [11]. Today there is no available tool capable of predicting whether or not a tumour will achieve a CR and no clear guidelines for treatment continuation. In this study, we further analysed data on POLA-BCC tumours from the STEVIE study to evaluate whether the initial treatment response could predict final outcome and help establish a treatment algorithm.

METHODS

Study design and patients

STEVIE is a single-arm, multicentre, open-label study involving 167 treatment locations in 36 countries. The study design and methods were described in detail elsewhere [8, 11]. The original STEVIE study design did not relate specifically to ocular tumour involvement or ocular function. Data mining techniques were utilized in order to construct an ophthalmic

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Table 1. Baseline Characteristics of POLA BCC.

Variable	≤10 mm	>10 mm and ≤20 mm	>20 mm and ≤30 mm	>30 mm	*P* Value
N	22	91	67	84	
Locally advanced	22 (100.0)	89 (97.8)	65 (97.0)	82 (97.6)	1
Metastatic	0 (0.0)	2 (2.2)	2 (3.0)	2 (2.4)	
Age (median [IQR])	67.00 [52.50, 82.00]	69.00 [59.00, 77.00]	76.50 [58.25, 82.75]	74.00 [61.00, 83.00]	0.213
Male (%)	9 (40.9)	56 (61.5)	39 (58.2)	50 (59.5)	0.373
Gorlin (%)	6 (27.3)	22 (24.4)	8 (11.9)	4 (4.8)	0.001
Histologically confirmed (%)	22 (100.0)	91 (100.0)	66 (98.5)	83 (98.8)	0.604
Time since initial diagnosis (years) (median [IQR])	6.36 [2.57, 21.36]	11.53 [5.02, 18.08]	8.49 [2.28, 15.82]	7.6 [2.42, 16.46]	0.254
Time since initial diagnosis of Gorlin (years) (median [IQR])	8.14 [4.08, 27.6]	17.62 [5.26, 34.25]	26.67 [16.16, 30.21]	31.08 [23.53, 34.6]	0.656
Baseline diameter (median [IQR])	10.00 [10.00, 10.00]	15.00 [13.00, 19.00]	26.00 [25.00, 30.00]	47.00 [36.00, 60.00]	<0.001
Final diameter (median [IQR])	0.00 [0.00, 4.50]	0.00 [0.00, 12.00]	10.00 [0.00, 20.00]	26.50 [0.00, 42.50]	<0.001
Day of final diameter (median [IQR])	174.50 [112.25, 418.75]	291.00 [171.00, 589.50]	282.00 [184.50, 659.50]	289.00 [155.50, 535.75]	0.379
Treatment cycles (median [IQR])	7.00 [3.50, 14.00]	11.00 [5.50, 19.50]	11.00 [7.00, 24.00]	11.00 [6.00, 19.25]	0.525
Measurable disease	22 (100.0)	91 (100.0)	67 (100.0)	84 (100.0)	NA
Operability of locally advanced disease					
Inoperable	6 (27.3)	34 (38.2)	25 (38.5)	33 (40.2)	0.763
Surgery is medically contraindicated	16 (72.7)	55 (61.8)	40 (61.5)	49 (59.8)	0.763
Surgery is unlikely to be curatively resected (%)	7 (100.0)	22 (100.0)	20 (100.0)	16 (100.0)	NA
Anticipated substantial morbidity and/or deformity from surgery (%)	9 (100.0)	36 (100.0)	27 (100.0)	33 (100.0)	NA
Radiotherapy administered to at least one lesion	5 (22.7)	21 (23.3)	20 (29.9)	26 (31.0)	0.635
Radiotherapy not administered: reason					
Contraindicated	7 (41.2)	34 (49.3)	19 (40.4)	25 (43.1)	0.785
Inappropriate	10 (58.8)	35 (50.7)	28 (59.6)	33 (56.9)	
Tumour follow-up by imaging (%)	3 (13.6)	22 (24.2)	14 (20.9)	18 (21.4)	0.79

IQR Interquartile range, *mm* Millimetre, *CR* Complete response, *PR* Partial response, *PD* Progressive disease, *SD* Stable disease, *NE* Not evaluable.

database from the STEVIE study population. Ophthalmic involvement was identified by applying a natural-language-processing (NLP) search for anatomical ophthalmic key words. Each identified ocular tumour was evaluated by an oculoplastic specialist for validation and given a study tumour identification number. Further assessment according to the response evaluation criteria in solid tumours (RECIST) of target lesions vs. non-target lesions was carried out, and only patients with target lesions (i.e., those with the longest diameter and suitability for accurate repeated measurements) were included in the analysis. Target lesions were measured in millimetres (mm) by either external investigator measurements or by imaging studies (computerized tomography [CT] or magnetic resonance imaging [MRI]).

The tumours were categorized into groups 1 to 4, based on their diameter size. Group 1 ≤ 10 mm, group 2 > 10 and ≤20 mm, group 3 > 20 and ≤30 mm, and group 4 > 30 mm.

Response to treatment was analysed for all tumours, compared between the groups of different sizes, and evaluated by 3 methods. First, the absolute size (in mm) over time was assessed along the entire study. Second, the best overall response for each tumour was extracted from the investigator-assessed objective response according to RECIST v 1.1 (CR, PR, progressive disease [PD], and stable disease [SD]) [12].

Statistical analysis

Patient demographic and clinical data were evaluated with descriptive statistics to compare baseline and follow-up characteristics. Analyses of covariance statistics assessed the observed differences between the groups. The Mann-Whitney U test or the Kruskal-Wallis test was applied when appropriate. The Wilcoxon signed-rank test was applied for paired samples, and the chi-square or Fisher's exact test was applied as suitable for nominal variables. Multiple comparisons were adjusted according to the Bonferroni correction. Correlations between continuous variables were analysed by the Pearson correlation coefficient and by the Spearman correlation coefficient for binomial variables. A receiver operating characteristic (ROC) analysis determined the optimal value of specific characteristics for the prediction of a CR. A logistic multivariate analysis identified factors relevant to the prediction of a CR among the vismodegib-treated patients. Estimations are given as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were 2-sided, and statistical significance was set at a *P*-value of 0.05. Statistical analysis was with Prism version 7 and R version 3.4.2 (R Development Core Team 2017).

RESULTS

Patient demographics and characteristics

In total, 1232 patients were enrolled between June 30, 2011, and June 14, 2017. At study completion, 1215 patients had received at least 1 dose of the study drug. A total of 264 target tumours were located in the periocular area in 244 patients. Of those tumours, 258 (96.7%) had LA-BCC and 6 (2.3%) had metastatic BCC. The tumours were divided for follow-up by clinical measurements ($n = 180$, 68%) or by CT or MRI studies ($n = 84$, 32%) (Table 1).

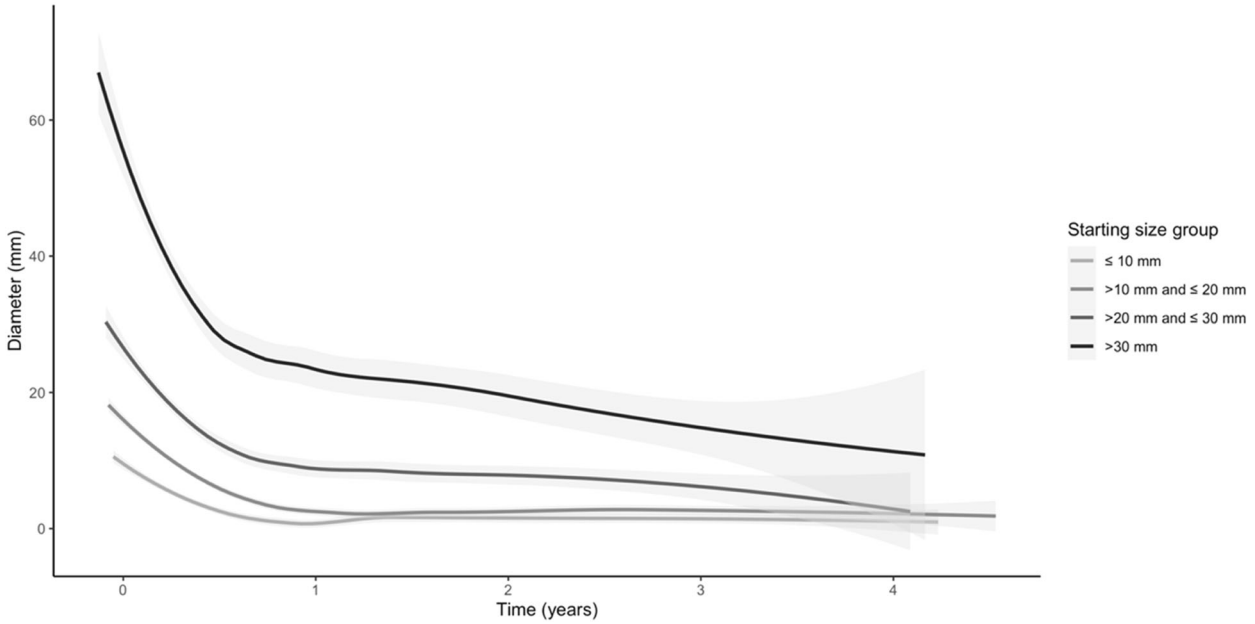

Fig. 1 Change in tumour size during the study. Change in tumour size over time. Trends of the different tumour sizes according to LOESS regression.

Table 2. Tumour outcome of POLA BCC.

Variable	≤10 mm	>10 mm and ≤20 mm	>20 mm and ≤30 mm	>30 mm	*P* Value
N	22	91	67	84	
Size at end of study, mm (%)					
0	13 (59.1)	47 (51.6)	24 (35.8)	26 (31.0)	0.01
≤10	8 (36.4)	20 (22.0)	12 (17.9)	5 (6.0)	0.001
>10 and ≤20	1 (4.5)	24 (26.4)	16 (23.9)	8 (9.5)	0.005
>20 and ≤30	0 (0.0)	0 (0.0)	12 (17.9)	13 (15.5)	<0.001
>30	0 (0.0)	0 (0.0)	3 (4.5)	32 (38.1)	<0.001
Best overall response					
CR (%)	12 (54.5)	36 (39.6)	19 (28.4)	19 (22.6)	0.011
PR (%)	7 (31.8)	30 (33.0)	27 (40.3)	34 (40.5)	0.66
PD (%)	0 (0.0)	0 (0.0)	0 (0.0)	7 (8.3)	0.002
SD (%)	1 (4.5)	16 (17.6)	15 (22.4)	18 (21.4)	0.254
NE (%)	0 (0.0)	1 (1.1)	1 (1.5)	0 (0.0)	0.780

CR Complete response, *PR* Partial response, *PD* Progressive disease, *SD* Stable disease, *NE* Not evaluable.

Tumour characteristics

The initial group size category distribution was 22 (8.3%) tumours in group 1 (<10 mm), 91 (33.7%) tumours in group 2 (>10 mm and ≤20 mm), 67 (25.0%) tumours in group 3 (>20 mm and ≤30 mm), and 84 (39.0%) tumours in group 4 (>30 mm). Metastatic BCC accounted for 6 (2.45%) tumours, with 2 tumours in groups 2, 3, and 4 each, and none in group 1. The initial distribution of tumour size as evaluated by imaging (68%) was fairly similar across the total POLA-BCC population: 3 tumours (13.6%) in group 1, 22 tumours (24.2%) in group 2, 14 (20.9%) tumours in group 3, and 18 tumours (21.4%) in group 4.

Tumour response to treatment

Most tumours (92.4%) responded to treatment and showed absolute reduction in size after treatment. A similar trend towards tumour reduction was observed among the different groups (Fig. 1), with the greatest reduction in tumour diameter occurring during the first year ($P < 0.0001$). Groups 1 and 2 showed a significantly better absolute reduction in size (72.7% for group 1 and 64.7% for group 2) compared to group 4 (47.5%, $P = 0.009$ and $P = 0.006$ respectively, Mann-Whitney test) (Supplemental Fig. 1). Tumour response according to RECIST was evaluated for each group, and it revealed that group 1 (54.5%) had more tumours that achieved CR compared to groups 3 (28.4%) and 4 (22.6%) ($P = 0.004$ and $P = 0.003$, respectively). Similarly, group 2 (39.6%) exhibited more CR compared to group 4 ($P = 0.004$). There was no group difference for PR (31.8%, 33.0%, 40.3%, and 40.5%, respectively, $P = 0.66$). PD was observed only in the group 4 tumours which were larger than 30 mm ($P = 0.002$) (Table 2).

Predictive Model for Treatment

An ROC analysis was used at 3 and 6 months of treatment in order to identify a cutoff value of tumour size reduction that could serve as a measure to distinguish between tumours that achieve a CR compared to all other outcomes. At 3 months, the best cutoff value to distinguish between CR outcomes compared to all other

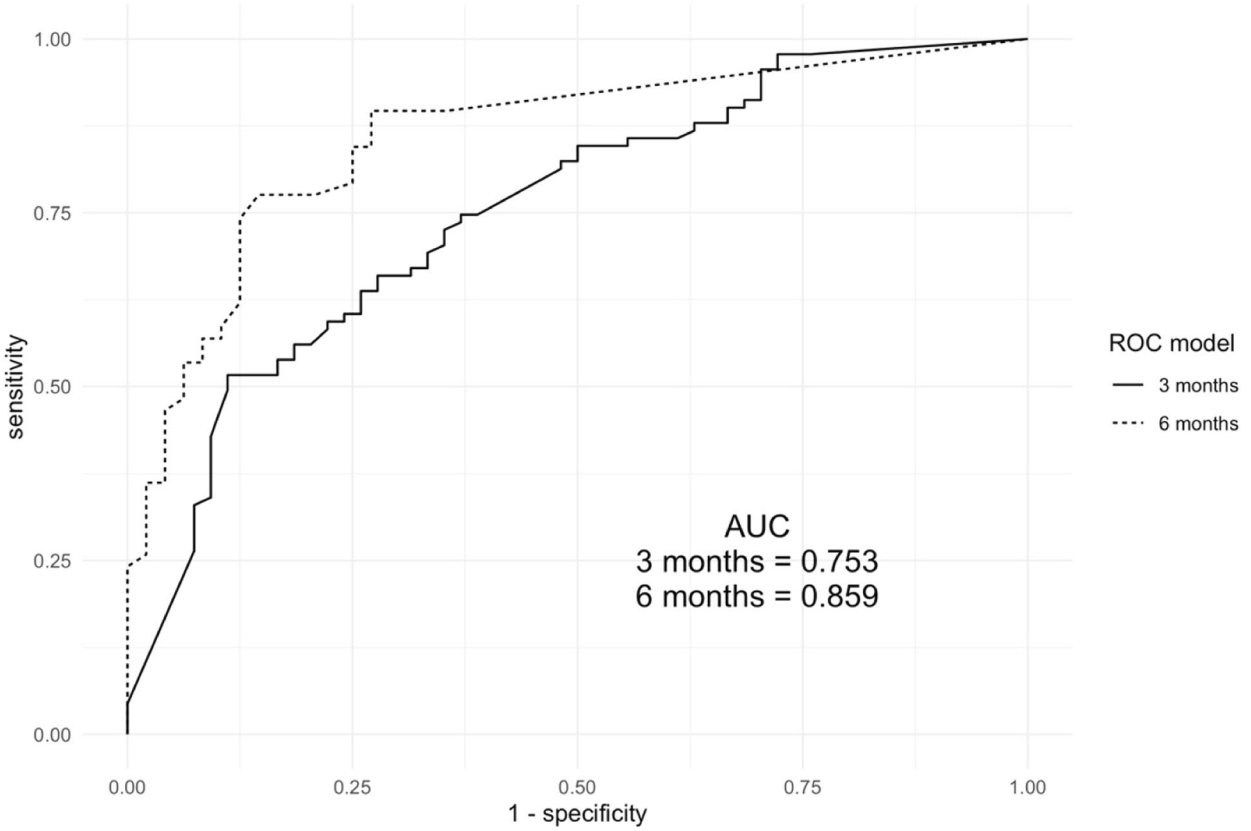

Fig. 2 ROC curve for reduction in size at 3, and 6 months. ROC curves by size reduction at 3 and 6 months, CR Complete response, AUC Area under the curve.

types of response was 20% in tumour size reduction. This cutoff value produced a sensitivity of 51.64% (95%CI 41.76–61.54%) and a specificity of 85.18% (95%CI 75.93–94.44%) (AUC = 0.753). At 6 months, the best cutoff value was a reduction of 67.7% with a sensitivity of 77.58% (95%CI 66.67–95.82%) and a specificity of 85.41% (95%CI 68.97–94.87%)(AUC = 0.859) (Fig. 2).

Multivariant Analysis

First, a multivariate analysis was conducted in order to assess predictors for CR. When compared to small tumours of group 1, all larger groups had a decreased odds of achieving CR: (group 2: OR = 0.309, 95%CI 0.095–0.937, $P = 0.042$; group 3: OR = 0.242, 95% CI 0.071–0.772, $P = 0.019$; group 4: OR = 0.18, 95%CI 0.053–0.570, $P = 0.004$). Furthermore, previous administration of radiotherapy decreased the odds for achieving a good overall response rate by 19.89%, (95%CI 0.100–0.574, $P = 0.002$). Additionally, the number of treatment cycles increased the odds by 3% (95%CI 1.000–1.060, $P = 0.04$). Other variables of sex, age, metastatic disease, Gorlin syndrome, time from initial diagnosis, and initial diameter had no statistically significant effect on achieving CR (Supplemental Table 1). Second, an adjusted multivariate logistic regression model corresponding to the cutoff values detected by the ROC analysis at 3 and 6 months of treatment were applied in order to assess the probability to achieve a CR outcome. At 3 months of follow-up, a reduction in tumour size of more than 20% yielded an 82.76% probability for a CR (OR = 4.8, $P = 0.003$, 95%CI 1.740–14.930) compared to only a 17.24% probability for a CR (OR = 0.2, $P = 0.003$, 95%CI 0.060–0.570) for tumours reduced in size by less than 20% at 3 months. At 6 months of follow-up, a reduction of more than 67.7% produced a probability of 95.42% for CR (OR = 20.87, 95%CI 6.760–77.770, $P < 0.001$). Tumours that had less than a 67.7% reduction in size at 6 months had a probability of only 4.58% to achieve a CR (OR = 0.04, 95%CI 0.010–0.140, $P < 0.001$,).

DISCUSSION

The objective of this subgroup analysis of the POLA-BCC tumours from the STEVIE study was to analyse the response to vismodegib treatment over time. The results demonstrated that over time, 92% of the tumours showed a reduction in size following treatment. Most of the reduction in tumour size occurred during the first year of treatment ($P < 0.0001$), and continued to a much lesser extent into the second and third years. This pattern of reduction in size was consistent in all 4 size groups, even for very large and advanced tumours.

Analysis of tumour size over time enabled us to develop a tumour behaviour prediction model based on the probability of CR as final outcome. This model can improve decision-making and guidance in planning further management. By applying the ROC analysis, we identified optimal cutoff values of tumour size reduction at several time points that differentiated between 2 types of tumours' behaviour. The "slow response" tumours (<20% regression at 3 months or <67.7% regression at 6 months) that are not expected to achieve a CR outcome, and the "rapid response" tumours (>20% regression at 3 month or >67.7% at 6 months) that are highly likely to achieve a CR outcome. These "slow response" tumours had a probability of only 17.24% for a CR at 3 months and barely 5% at 6 months, while "rapid response" tumours had an 82.76% probability for a CR outcome at 3 months and 95.42% at 6 months. (Fig. 3).

These findings facilitated the development of a treatment algorithm based on the probability to achieve CR. The "slow response" tumours bearing a low probability to achieve CR can be offered 1 of 2 strategies as early as 3–6 months: either switching from a full-dosage protocol to a more tolerable extended protocol of vismodegib, or adding surgery or radiotherapy to the vismodegib protocol. An extended treatment protocol is intended to reduce the severity of side effects and increase tolerability while

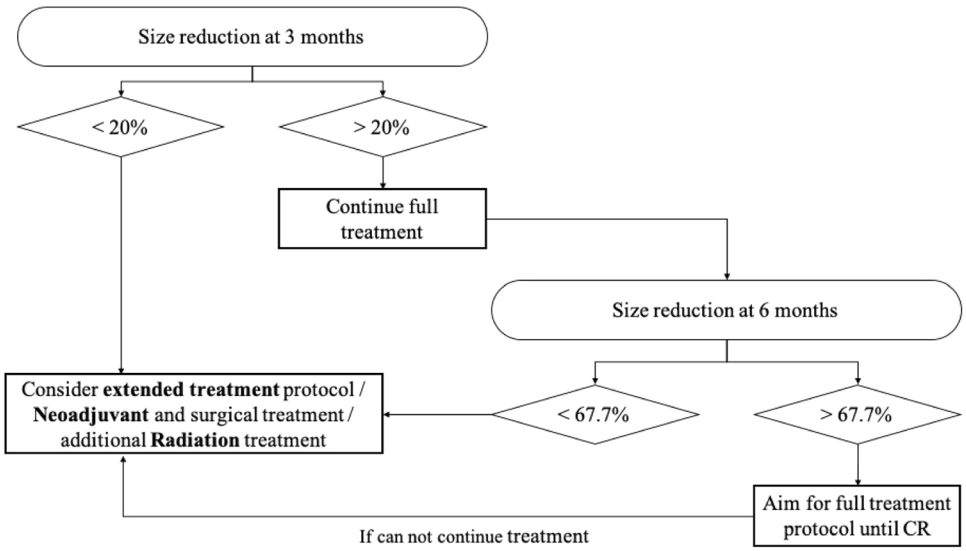

Fig. 3 Decision algorithm during treatment. Decision algorithm based on treatment response at 3 and 6 months.

maintaining treatment efficacy over a long period of time and include long-term intermittent dosing, as described in the MIKIE study [13], or a maximally tolerated medical treatment specific for each patient, including the use of partial doses on alternate days and multiple "drug holidays", as reported for 21 POLA patients by Eiger-Moskovitch and colleagues [14]. The second strategy for tumour control in "slow response" tumours is to consider the use of Vismodegib as a *de-facto* neoadjuvant treatment prior to surgery or radiotherapy, based on the prediction that CR will not be achieved by vismodegib alone [15–20]. These patients may still be candidates for curative mutilating surgery (exenteration, partial exenteration, or resection of a large portion of the eyelid and eye-preserving approaches) as a means to achieve cure [21–23]. It should be borne in mind that the neoadjuvant use of vismodegib prior to surgery or radiation treatment, although gaining in popularity, is still considered off-label use [24].

On the other hand, patients with a "rapid response" tumour should be encouraged to adhere to the standard full-dose treatment due to the high likelihood of a CR. Side effects should be addressed as effectively as possible in recognition of their being the main reason for treatment discontinuation [9, 11]. Most side effects are of grade 1 or 2 in severity and can be successfully dealt with by standard means [9, 11]. Reassuring the patients that CR is likely may also improve compliance. Surgery should be considered only if side effects cannot be overcome or if CR is not achieved at a later stage as expected.

It must be emphasized that CR is a clinical term and does not necessarily mean histological CR. Both clinical and histological CR are difficult to assess in the scar tissue that replaces the shrinking tumour [18]. Still, achieving clinical CR is of major importance since the effect may be long-lasting. A recent French multicentre study on 116 patients with LA BCC who were diagnosed as having achieved a CR reported an average relapse-free survival of 18.4 months and a relapse-free survival rate of 35.4% at 36 months [25]. Reports specific to the ocular area showed similar results [14].

Several limitations in our study bear mention. The STEVIE study had not been designed to address specific ophthalmic issues. While data on tumour size were collected meticulously, the specific location relative to ocular structures, such as eyelid margin or orbital septum, was not provided. This omission of information precluded a direct match to the AJCC 8th edition. Additionally, data of significant importance for ophthalmologists regarding ocular function and vision were not collected as part of study design and therefore could not be correlated to tumour regression. The issue of visual preservation awaits further study [26]

In conclusion, we were able to develop a model for predicting a CR outcome based on the initial response to treatment by vismodegib and to establish a treatment algorithm based on this model. A cutoff value of 20% and 67.7% reduction in tumour size at 3 and 6 months, respectively, distinguished between "rapid response" tumours that have a high probability (82.76% and 95.42% respectively) to achieve CR from " slow response" tumours that have a low probability (17.24% and 4.58% respectively) for a CR outcome. The aim to continue full treatment protocol is warranted for "rapid response" tumours while a change in protocol or treatment should be considered for "slow response" tumours. Furthermore, we demonstrated a correlation between tumour size and vismodegib treatment outcome in this subgroup analysis of POLA-BCC tumours from the STEVIE study. Additional adjusted risk factors that affected outcome were previous radiation and fewer treatment cycles. We believe that the results of this study provide important new insights which offer the treating oncologist and ophthalmologists additional valuable tools for managing these complicated POLA-BCC tumours.

Summary

What was known before

- Locally advanced basal cell carcinoma accounts for more than 90% of the most advanced and complicated periocular tumours. Vismodegib (ErivedgeTM) is currently considered the treatment of choice for this condition. Our group has reported on some of the largest cohorts and case series on the subject which have helped to establish solid evidence-based data on treatment outcomes. Until now, however, there has not been any tool capable of predicting whether or not a tumour will achieve a complete response, nor have there been any clear-cut guidelines for therapeutic management.

What this study adds

- A treatment model was constructed based on the prediction of a CR outcome and the initial response to vismodegib treatment at 3 and 6 months. The study result provide significant new insights can facilitate decision-making on

treatment management according to tumour response in patients with POLA BCC

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AUTHOR CONTRIBUTIONS

AT and IY had the initial idea and participated in article preparation, AT performed data preparation and analysis and wrote the paper, MBI participated in data preparation. EF, GBS, and MBI participated in article preparation. All authors have approved the final article.

COMPETING INTERESTS

Dr. Fenig reported serving as an investigator in the Safety Events in Vismodegib (STEVIE) study. No other disclosures were reported.

ADDITIONAL INFORMATION

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