Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial

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Summary

Background Vismodegib, a first-in-class Hedgehog-pathway inhibitor, is approved for use in adults with advanced basal-cell carcinoma. Patients with multiple basal-cell carcinomas, including those with basal-cell nevus (Gorlin) syndrome, need extended treatment. We assessed the safety and activity of two long-term intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas.

Methods In this randomised, regimen-controlled, double-blind, phase 2 trial, we enrolled adult patients with multiple basal-cell carcinomas, including those with basal-cell nevus syndrome, who had one or more histopathologically confirmed and at least six clinically evident basal-cell carcinomas. From a centralised randomisation schedule accessed via an interactive voice or web-based response system, patients were randomly assigned (1:1) to treatment group A (150 mg oral vismodegib per day for 12 weeks, then three rounds of 8 weeks of placebo daily followed by 12 weeks of 150 mg vismodegib daily) or treatment group B (150 mg oral vismodegib per day for 24 weeks, then three rounds of 8 weeks of placebo daily followed by 8 weeks of 150 mg vismodegib daily). Treatment assignment was stratified by diagnosis of basal-cell nevus syndrome, geographical region, and immunosuppression status. The primary endpoint was percentage reduction from baseline in the number of clinically evident basal-cell carcinomas at week 73. The primary analysis was by intention to treat. The safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01815840, and the study is ongoing.

Findings Between April 30, 2013, and April 9, 2014, 229 patients were randomly assigned treatment, 116 in treatment group A and 113 in treatment group B. The mean number of basal-cell carcinoma lesions at week 73 was reduced from baseline by 62·7% (95% CI 53·0–72·3) in treatment group A and 54·0% (43·6–64·4) in treatment group B. 216 (95%) of 227 patients included in the safety analysis had at least one treatment-emergent adverse event deemed to be related to study treatment (107 [94%] of 114 in treatment group A and 109 [97%] of 113 in treatment group B). The most common grade 3 or worse treatment-related adverse events were muscle spasms (four [4%] patients in treatment group A *vs* 12 [11%] in treatment group B), increased blood creatine phosphokinase (one [1%] *vs* four [4%]), and hypophosphataemia (zero *vs* three [3%]). Serious treatment-emergent events were noted in 22 (19%) patients in treatment group A and 19 (17%) patients in treatment group B. Four (2%) patients died from adverse events; one (pulmonary embolism in treatment group A) was possibly related to treatment.

Interpretation Both intermittent dosing schedules of vismodegib seemed to show good activity in long-term regimens in patients with multiple basal-cell carcinomas. Further study is warranted.

Funding F Hoffmann-La Roche.

Introduction

Basal-cell carcinoma is the most commonly diagnosed human cancer, accounting for around 80% of all non-melanoma skin cancers.[1,2] Abnormal Hedgehog-pathway signalling is the key molecular driver of the development of basal-cell carcinoma, and is seen in more than 90% of cases. The role of abnormal Hedgehog-pathway signalling in cancer was first identified in patients with basal-cell nevus (Gorlin) syndrome.[2,3] Patients with this syndrome have a genetic predisposition to develop multiple basal-cell carcinomas from a young age, which can result in a substantial physical and psychological burden.[4]

Vismodegib is a small-molecule antagonist of the Hedgehog signalling pathway that binds to and inhibits Smoothened homologue (SMO), which prevents subsequent pathway signalling.[5] The pivotal phase 2 registration study, ERIVANCE BCC,[6] showed that 27 (43%) of 63 patients with locally advanced basal-cell carcinoma and ten (30%) of 33 patients with metastatic disease had objective responses to vismodegib when assessed by independent reviewers. The 30-month update from ERIVANCE BCC[7] confirmed consistency in treatment activity and safety profile, and showed a median duration of response of 26·2 months in patients with locally advanced basal-cell carcinoma.

Research in context

Evidence before this study

We searched MEDLINE and Embase with the search terms "basal cell carcinoma", "BCC", "vismodegib", "multiple BCC", and "Gorlin syndrome" for peer-reviewed articles and abstracts published from Jan 1, 2010, to Oct 1, 2016. Most investigations of vismodegib in clinical trials have been in patients with advanced basal-cell carcinoma. The pivotal ERIVANCE BCC phase 2 trial also included patients with multiple basal-cell carcinomas, including some with basal-cell nevus (Gorlin) syndrome, and showed clinical benefit in this population. Another study by Tang and colleagues showed the efficacy of vismodegib versus placebo in managing basal-cell carcinoma in patients with basal-cell nevus syndrome. Nevertheless, chronic low-grade toxic effects make long-term treatment intolerable for most patients. Therefore, there is a high unmet need for long-term efficacious treatments for patients with multiple basal-cell carcinomas and basal-cell nevus syndrome.

Added value of this study

To the best of our knowledge, the MIKIE study includes the largest population of patients with basal-cell nevus syndrome and multiple basal-cell carcinomas so far. We investigated whether an intermittent regimen of vismodegib could balance activity and toxicity so that growth of basal-cell carcinomas would be inhibited, while improving the overall tolerability to limit the number of patients who discontinued treatment. The primary analysis shows that intermittent dosing of vismodegib was efficacious and tolerable in patients with multiple basal-cell carcinomas. Patients showed meaningful clinical benefit in both treatment groups. The safety profiles of the two regimens were similar, and the range of adverse events was consistent with previous clinical experience.

Implications of all the available evidence

Our results suggest that intermittent dosing schedules could be useful for patients with multiple basal-cell carcinomas who need long-term treatment.

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On the basis of these results, vismodegib was approved by the US Food and Drug Administration in January, 2012, and by the European Medicines Agency in July, 2013, for the treatment of adults with metastatic basal-cell carcinoma or locally advanced basal-cell carcinoma that was unsuitable for surgery or radiotherapy.[8,9] The activity and safety profiles for vismodegib have since been strongly corroborated.[7,10,11] Another Hedgehog-pathway inhibitor, sonidegib, has also been approved for use in patients with locally advanced basal-cell carcinoma.[12]

Vismodegib was assessed in a randomised, double-blind, placebo-controlled, phase 2, investigator-sponsored study in 42 patients with basal-cell nevus syndrome.[13] Tumour burden and growth of basal-cell carcinomas were reduced in patients with basal-cell nevus syndrome. However, chronic low-grade toxic effects led about half of the patients to discontinue vismodegib within 12 months of starting treatment.

A high unmet need remains in the management of basal-cell carcinoma in patients who require long-term treatment. Clinical studies of vismodegib have allowed treatment interruptions as a means of managing toxic effects.[7,11] An intermittent dosing regimen might, therefore, benefit patients who need long-term treatment by providing a balance between treatment activity and toxicity and limit the number who stop treatment. In the MIKIE study, we assessed two long-term intermittent vismodegib dosing regimens in patients who had multiple basal-cell carcinomas, including those with basal-cell nevus syndrome. Here, we report the safety and activity results from the primary analysis.

Methods

Study design and patients

MIKIE was a randomised, double-blind, regimen-controlled, phase 2 study of vismodegib, done in 52 hospitals or clinics in ten countries: Austria, Canada, France, Germany, Italy, Mexico, Netherlands, the Russian Federation, Spain, and the USA (appendix pp 6–8). The study protocol is available in the appendix. Eligible patients were adults (age ≥18 years) with multiple basal-cell carcinomas amenable to surgery, including those with basal-cell nevus syndrome. We excluded patients who had locally advanced basal-cell carcinoma unsuitable for surgery or radiation or who had metastatic basal-cell carcinoma. Patients had to have six or more clinically evident basal-cell carcinomas (three measuring at least 5 mm in diameter, of which at least one was histologically confirmed, were designated target lesions), an Eastern Cooperative Oncology Group performance status score of 0–2, adequate organ function, and a negative serum test for pregnancy. Patients participating in another drug study had to have discontinued treatment more than 28 days before enrolment. Patients with uncontrolled medical illness or history of other disease that might affect interpretation of the study results were excluded.

See Online for appendix

Life expectancy in the study population was deemed to be similar to that of the general population because enrolled patients did not have metastatic or locally advanced tumours. Furthermore, life expectancy of patients with basal-cell nevus syndrome does not differ from the average life expectancy of the general population.[14]

The study was undertaken in accordance with the principles of the Declaration of Helsinki and Good

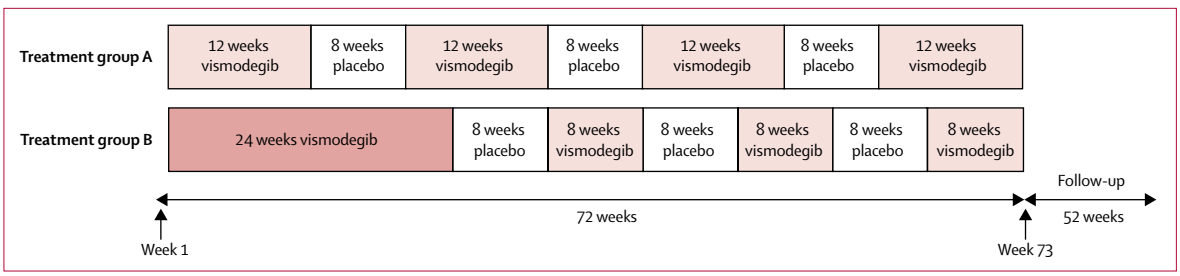

Figure 1: **Treatment schedules**

Clinical Practice guidelines. Ethics approval was obtained from the institutional review board or ethics committee and competent authority at each study site before the study was started. Patients' safety during the study was assessed by an independent data safety monitoring board. All patients provided written informed consent to participate and for photographs to be taken of target lesions.

Randomisation and masking

Enrolled patients were randomly assigned (1:1) with a centralised randomisation process to receive one of two intermittent dosing schedules. The computer-generated randomisation schedule was stratified by diagnosis of basal-cell nevus syndrome (yes *vs* no), geographical region (Europe *vs* the Americas), and immunosuppression status. Treatment was assigned randomly by a dynamic randomisation process with an imbalance threshold between groups of three patients per stratum and, in case the imbalance threshold was met, probability of 75% for assignment of the patient to the group with the smaller number of patients. The next allocation was obtained via an interactive voice or web-based response system. Patients and investigators were masked to treatment assignment by use of placebo capsules with the same physical characteristics and composition as vismodegib, minus the active pharmaceutical ingredient.

Procedures

Patients in treatment group A received 150 mg oral vismodegib per day for 12 weeks, then three rounds of 8 weeks of placebo daily followed by 12 weeks of 150 mg vismodegib daily (figure 1). This regimen was based on a study of patients with basal-cell nevus syndrome in which more than 90% tolerated 12 weeks of vismodegib therapy and had minimum regrowth of basal-cell carcinomas in the 8 weeks after treatment was stopped.[13] Patients in treatment group B received oral vismodegib 150 mg per day for 24 weeks, then three rounds of 8 weeks of placebo daily followed by 8 weeks of 150 mg vismodegib daily (figure 1). This regimen was chosen to investigate whether intensive induction might improve disease control and permit a less intense treatment regimen thereafter. The overall treatment phase was 72 weeks in both groups and resulted in similar planned total drug exposure (ie, 48 weeks of vismodegib and 24 weeks of placebo). 4 weeks of treatment represented one treatment cycle. No dose reductions were allowed, but treatment interruptions for up to 2 weeks were permitted to manage toxic effects or temporary inability to swallow capsules, up to a total of 4 weeks within the whole treatment phase. After the final visit at the end of treatment (week 73), patients who did not withdraw consent were followed up for an additional 52 weeks; follow-up data from this period are not reported in this Article.

Patients' adherence to treatment was assessed by recording the dispensing of study drug and through patients recording in diaries occasions when any doses were missed. Investigators reviewed the diaries at each study visit. Investigators assessed tumour responses by physical examination and counts of basal-cell carcinomas every 8 weeks. Laboratory haematology and biochemistry assessments were done every 8 weeks. Adverse events were assessed at visits every 4 weeks and classified with the Medical Dictionary for Regulatory Activities, version 18.0. Genomic mutations were assessed in the study population to investigate a correlation with response; results of these analyses will be reported elsewhere.

Outcomes

The primary endpoint was percentage reduction from baseline in the number of clinically evident basal-cell carcinomas at week 73. The secondary endpoints were tolerability, discontinuation of treatment, reduction in the total size of the three target lesions (based on the sum of the longest diameters), at least 50% reduction in number of basal-cell carcinomas, number of new basal-cell carcinomas at week 73, and disease recurrence. Exploraotry analyses of subgroups, including stratification factors, age, and sex, were also done post hoc.

Statistical analysis

We calculated that a sample size of 200 patients (100 per treatment group) would allow for computation of point estimates (produced by nQuery, version 7) and 95% CIs (based on *t*-distribution) for various possible differences between groups, ranging from 55% to 75%, with a precision of 5·9% and an SD of 30%. No power

calculation was done for any other endpoint. No formal statistical hypotheses for treatment comparisons were tested since the study was not designed to show a significant difference between treatment groups. We have reported 95% CIs and p values for all relevant estimates to enable an exploratory comparison between the two treatment groups. Final conclusions were based on per-group estimates and 95% CIs per treatment group.

The mean difference between treatment groups in the primary endpoint, along with two-sided 95% CIs, was estimated by fitting an ANCOVA model adjusted for the stratification factors (model A) and unadjusted (model B) . The primary analysis was done by intention to treat (all patients as randomised) and used the last observation carried forward method for imputation of missing data. A prespecified sensitivity analysis of the primary endpoint was also done on the per-protocol population (all patients who completed the study without major protocol violations, such as treatment interruption >4 weeks, patient receiving incorrect study treatment, no assessments at or after baseline for multiple basal-cell carcinomas, and meeting any exclusion criteria. Additionally, we analysed the primary endpoint in a modified intention-to-treat population that excluded patients who underwent surgery or medical intervention for non-target basal-cell carcinomas after week 32 of treatment, with additional imputation (worst case or average) or based on observed data; this analysis was also prespecified. Safety was assessed in all patients who received at least one dose of the study treatment. All statistical analyses were done with SAS version 9.2. This trial is registered with ClinicalTrials.gov, number NCT01815840.

Role of the funding source

The funder was involved in the study design, data collection, data analysis, data interpretation, and writing of the report, and had access to the raw data in the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 30, 2013, and April 9, 2014, 263 patients were screened, of whom 229 were randomly assigned to treatment group A (n=116) and treatment group B (n=113, figure 2). The two groups had similar clinical characteristics and demographics at baseline (table 1). Clinical cutoff, when the final patient completed 72 weeks of treatment, was Aug 27, 2015.

Of the 229 patients randomly assigned, 120 (52%) completed treatment and 137 (60%) entered the 1-year follow-up period (figure 2). Treatment was discontinued in 107 (47%) of 229 patients (50 [44%] of 116 in treatment group A and 57 [50%] of 113 patients in treatment group B). The main reason for discontinuation of study treatment was treatment-emergent adverse events in both treatment groups (figure 2). Withdrawal of consent was also similar in the two groups (figure 2).

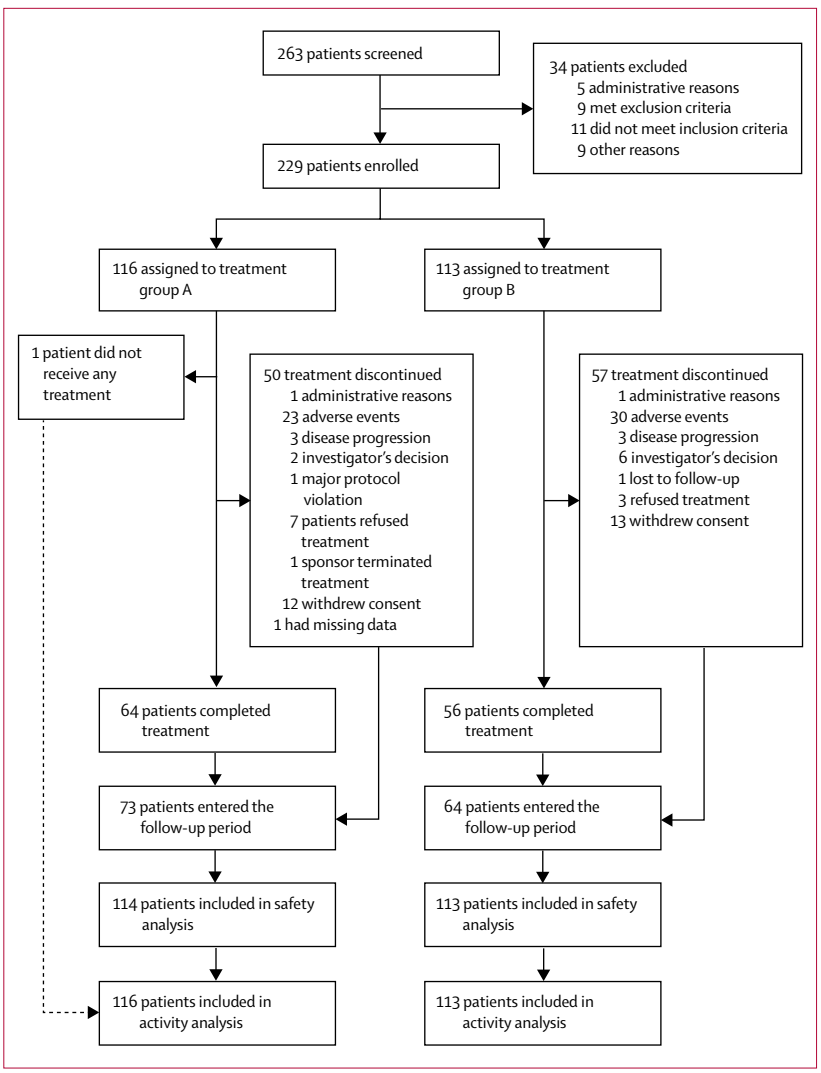

Figure 2: **Trial profile**

The median treatment duration was 71·4 weeks (range 1·3–73·3; 71·6 weeks [1·3–72·9] in treatment group A and 68·4 weeks [1·6–73·3] in treatment group B). Patients received a median of 18 4-week cycles of vismodegib and placebo (18 [IQR 5–18] in treatment group A and 17 [5–18] in treatment group B). 227 patients received at least one dose of vismodegib; two patients did not receive the drug because one patient was randomised twice by mistake and one patient withdrew consent. 111 (97%) of 114 patients in treatment group A and 107 (95%) of 113 in treatment group B fully adhered to the treatment regimens.

At baseline, the mean total number of basal-cell carcinomas was similar in the two groups (table 2). The mean relative reduction in the number of clinically evident basal-cell carcinomas from baseline to end of treatment was 62·7% (95% CI 53·0–72·3) in treatment

	Treatment group A (n=116)	Treatment group B (n=113)
Sex		
Male	81 (70%)	88 (78%)
Female	35 (30%)	25 (22%)
Women of childbearing potential	8 (23%)	10 (40%)
Age (years)	62 (27–89)	60 (27–91)
<65 years	63 (54%)	64 (57%)
≥65 years	53 (46%)	49 (43%)
Confirmed diagnosis of basal-cell nevus syndrome		
Yes	44 (38%)	41 (36%)
No	72 (62%)	72 (64%)
Geographical region		
North and South America	36 (31%)	35 (31%)
Europe	80 (69%)	78 (69%)
Immunosuppression status		
Immunocompetent	116 (100%)	112 (99%)
Immunosuppressed	0	1 (1%)
Baseline ECOG performance status score		
0	97 (88%)	93 (83%)
1	12 (11%)	14 (13%)
>1	1 (1%)	5 (5%)
Mean (SD) time since BCC diagnosis (months)	197·3 (151·3)	189·5 (163·9)
Diagnosis histologically confirmed		
Yes	107 (93%)	102 (90%)
No	8 (7%)	11 (10%)
BCC count	6 (4–102)	6 (2–66)
Multiple BCCs		
Yes	114 (99%)	113 (100%)
No	1 (1%)	0
Previous procedures related to BCCs		
Yes	105 (91%)	90 (80%)
Complex surgical excision	16 (14%)	5 (4%)
Cryotherapy	12 (10%)	8 (7%)
Mohs surgery	25 (22%)	24 (21%)
Other	23 (20%)	25 (22%)
Simple surgical excision	78 (68%)	67 (59%)
No	10 (9%)	23 (20%)
(Table 1 continues in next column)		
(Continued from previous column)		
Previous surgery not related to BCCs		
Yes	68 (59%)	63 (56%)
Cancer related	21 (18%)	16 (14%)
Non-cancer related	55 (48%)	53 (47%)
No	47 (41%)	50 (44%)
Post-treatment surgical procedure		
No	64 (55%)	58 (51%)
Yes	14 (12%)	13 (12%)
Cryotherapy	2 (14%)	0
Mohs surgery	0	2 (15%)
Other	4 (29%)	0
Simple surgical excision	8 (57%)	11 (85%)
Post-treatment systemic therapy		
Yes	3 (3%)	1 (1%)
No	74 (64%)	69 (61%)
Other post-treatment therapy for BCC		
Yes	7 (6%)	9 (8%)
No	68 (59%)	61 (54%)

Data are number (%) or median (range) unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. BCC=basal-cell carcinoma.

***Table 1*: Baseline characteristics, demographics, and post-treatment procedures in the intention-to-treat population**

group A and 54·0% (43·6–64·4) in treatment group B (table 2). Mean reduction in the number of lesions increased over time (figure 3). In an exploratory analysis, mean relative reduction did not differ significantly between groups (table 2). Analysis of this endpoint stratified by immunocompetence (only one patient was immunosuppressed; treatment group B) and by geographical region was consistent with the overall results, with no significant differences between treatment groups (mean relative reduction: immunocompetent patients –8·9, 95% CI –23·0 to 5·2, model A p=0·21, model B p=0·22; Europe region –8·1, –20·4 to 4·2, model A p=0·20, model B p=0·22; and America region –16·2, –51·7 to 19·3, model A p=0·37, model B p=0·38; appendix p 4). In patients with basal-cell nevus syndrome, there was no significant difference in the mean relative reduction from baseline in the total number of basal-cell carcinomas (2·1, 95% CI –28·8 to –33·0, model A p=0·89, model B p=0·87; appendix p 4). Among patients without basal-cell nevus syndrome, those in treatment group A had a greater mean relative reduction in the number of clinically evident basal-cell carcinomas than those in treatment group B (–15·4 [95% CI –28·8 to –1·9], model A p=0·025, model B p=0·032).

In an exploratory comparison, mean relative reductions in the sum of the longest diameters of the three target basal-cell carcinoma lesions was significantly different between treatment groups (table 2).

At the end of treatment, 76 (66%) of 116 patients in treatment group A and 57 (50%) of 113 patients in treatment group B had at least 50% reductions from baseline in the total number of basal-cell carcinomas and most patients had no new lesions at the end of treatment (table 2). As end of study data are not yet mature, the number of patients with recurrence is not yet estimable and will be published separately.

The per-protocol analyses of the primary and secondary endpoints are shown in table 3. A prespecified sensitivity analysis of the primary endpoint in the modified intention-to-treat population excluding patients who underwent surgery or medical intervention for non-target

	Treatment group A (n=116)	Treatment group B (n=113)	Difference between groups (95% CI)*	p value*
Number of basal-cell carcinoma lesions				
Mean (SD) number at baseline	9·8 (12·9)	9·1 (8·1)	NA	NA
Mean (SD) number at end of treatment	3·4 (4·5)	3·5 (3·8)	NA	NA
Mean relative reduction from baseline to end of treatment	62·7% (95% CI 53·0 to 72·3)	54·0% (95% CI 43·6 to 64·4)	−8·9% (−23·0 to −5·2)	Model A 0·21, model B 0·24†
Total size of three target basal-cell carcinoma lesions (mm)				
Mean (SD) at baseline	52·7 (33·0)	50·2 (39·0)	NA	NA
Mean (SD) at end of treatment	11·6 (22·1)	17·8 (31·7)	NA	NA
Mean relative reduction from baseline to end of treatment	82·9%	68·8%	−15·2% (−27·4 to −3·0)	0·015
Patients with ≥50% reduction in total number of basal-cell carcinoma lesions from baseline to end of treatment	76 (65·5%)	57 (50·4%)	−15·1% (−27·7 to −2·4)	Not formally tested
Patients without new basal-cell carcinoma lesions at end of treatment‡	72 of 94 (76·6%)	64 of 86 (74·4%)	−2·2% (−14·8 to 10·4)	Not formally tested

NA=not applicable. *Exploratory analysis, as the study was not powered to compare groups. †ANCOVA model A was adjusted for stratification factors and model B was not adjusted for stratification factors. ‡Some patients were assessed before the end of the study due to discontinuing treatment early.

***Table 2*: Primary and secondary treatment activity outcomes in the intention-to-treat population**

basal-cell carcinomas after week 32 of treatment was consistent with the primary analysis (appendix p 5).

227 patients were included in the safety analysis (table 4). 107 (94%) of 114 patients in treatment group A and 109 (97%) of 113 patients in treatment group B had an adverse event deemed to be related to study treatment. The most common grade 3 or worse treatment-related adverse events were muscle spasms (four [4%] patients in treatment group A *vs* 12 [11%] in treatment group B), increased blood creatine phosphokinase (one [1%] *vs* four [4%]), and hypophosphataemia (zero *vs* three [3%]; table 4). All grade 3–5 events are reported in the appendix (pp 1–3). The most frequently reported treatment-emergent adverse events leading to discontinuation of study treatment were muscle spasm (seven [6%] of patients in treatment group A *vs* 14 [12%] in treatment group B) and dysgeusia (four [4%] *vs* nine [8%]).

Serious treatment-emergent adverse events deemed to be related to vismodegib treatment were reported in eight (4%) of 227 patients (table 5). In treatment group A these were increased liver enzyme concentration, increased platelet count, acute pancreatitis, asthenia, arthralgia, and pulmonary embolism (all n=1). In treatment group B one patient had pseudolymphoma and one had dehydration and lethargy. Four (2%) of 227 patients (two in each treatment group) died due to a treatment-emergent adverse event (table 5). The causes of death were pulmonary embolism (one patient in each treatment group), cardiogenic shock (one patient in treatment group B), and pneumonia (one patient in treatment group A). The latter patient developed pneumonia 70 days after completing treatment. Only the pulmonary embolism in the patient in treatment group A was suspected of being related to study treatment by the study investigator, although other causes are possible, such as reduced activity after surgery to remove a congenital benign cyst of the third ventricle that was detected on study day 177.

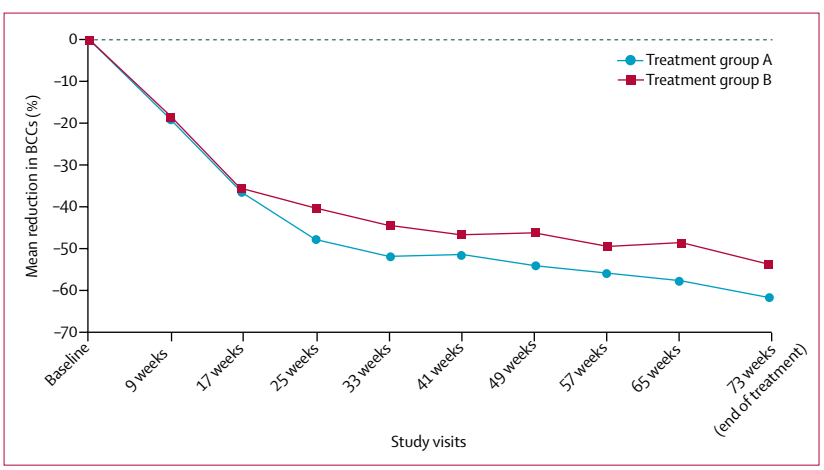

***Figure 3*: Mean percentage reduction from baseline in the number of clinically evident basal-cell carcinomas**
All patients who received treatment are included at all timepoints (treatment group A, n=114; treatment group B, n=113). Each treatment cycle was 4 weeks. BCCs=basal cell carcinomas.

Discussion

The primary analysis of the MIKIE study showed that both intermittent regimens controlled disease for the entire treatment period in most patients. In the intention-to-treat population, results for the primary endpoint did not differ between treatment groups, although, a significant difference was seen between treatment groups in the subgroup of patients without basal-cell nevus syndrome. Tumour shrinkage was similar in both treatment groups between the week 9 (end of cycle two) and week 17 (end of cycle four) study visits when patients in treatment group A were receiving their first 8-week course of placebo and patients in treatment group B were still receiving vismodegib as part of the initial 24-week course. This continuation of activity in treatment group A might be due to the half-life of vismodegib, the kinetics of tumour response, or both. The potential mechanisms will

	Treatment group A (n=59)	Treatment group B (n=48)	Difference between groups (95% CI)*	p value for difference*
Total number of basal-cell carcinoma lesions				
Mean (SD) at baseline	11·1 (17·6)	9·1 (9·2)	NA	NA
Mean (SD) at end of treatment	2·5 (4·7)	2·3 (3·0)	NA	NA
Mean relative reduction from baseline to end of treatment	72·7% (95% CI 56·8 to 88·6)	64·4% (95% CI 45·3 to 83·4)	−6·8% (−31·1 to 17·6)	Model A 0·58, model B 0·54†
Total size of three target basal-cell carcinoma lesions				
Mean (SD) at baseline (mm)	51·3 (32·4)	49·4 (37·2)	NA	NA
Mean (SD) at end of treatment (mm)	8·5 (19·0)	13·1 (25·0)	NA	NA
Mean relative reduction from baseline to end of treatment	87·8%	77·3%	−11·5% (−22·3 to −0·7)	0·037
Patients with ≥50% reduction in total number of basal-cell carcinoma lesions from baseline to end of treatment	49 (83·1%)	37 (77·1%)	−6·0% (−21·2 to −9·3)	Not formally tested
Patients without new basal-cell carcinoma lesions at end of treatment	44 (74·6%)	37 (77·1%)	−2·5% (−13·8 to 18·8)	Not formally tested

NA=not applicable. *Exploratory analysis, as the study was not powered to compare groups. †ANCOVA model A adjusted for and model B not adjusted for stratification factors.

***Table 3*: Primary and secondary treatment activity outcomes in the per-protocol population**

	Treatment group A (n=114)			Treatment group B (n=113)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
All	113 (99%)	30 (26%)	3 (3%)	110 (97%)	36 (32%)	4 (4%)
Muscle spasm	79 (69%)	4 (4%)	0	81 (72%)	12 (11%)	0
Dysgeusia	74 (65%)	1 (1%)	0	73 (65%)	2 (2%)	0
Alopecia	72 (63%)	0	0	73 (65%)	0	0
Fatigue	24 (21%)	0	0	26 (23%)	0	0
Weight decreased	23 (20%)	1 (1%)	0	21 (19%)	0	0
Decreased appetite	21 (18%)	0	0	15 (13%)	2 (2%)	0
Diarrhoea	20 (18%)	0	0	17 (15%)	1 (1%)	0
Nausea	23 (20%)	0	0	14 (12%)	1 (1%)	0
Asthenia	15 (13%)	0	0	19 (17%)	1 (1%)	0
Arthralgia	18 (16%)	0	0	16 (14%)	0	0
Myalgia	18 (16%)	0	0	12 (11%)	0	0
Ageusia	14 (12%)	0	0	12 (11%)	1 (1%)	0
Headache	11 (10%)	0	0	12 (11%)	0	0
Blood creatine phosphokinase increased	10 (9%)	1 (1%)	0	11 (10%)	4 (4%)	0
Pneumonia	0	2 (2%)	0	2 (2%)	0	0
Hypophosphataemia	0	0	0	0	3 (3%)	0
γ-Glutamyltransferase increased	0	2 (2%)	0	4 (4%)	0	0
Abscess limb	1 (1%)	0	0	1 (1%)	2 (2%)	0

Adverse events were classified with the Medical Dictionary for Regulatory Activities, version 18.0. Grade 1–2 events reported in ≥10% of patients and all grade 3–4 events that occurred in at least two patients are shown. All grade 3–5 adverse events are shown in the appendix (pp 1–3).

***Table 4*: Summary of treatment-emergent adverse events**

be addressed in a separate publication focusing on pharmacokinetic results. Notably, relative reductions in total size of three target lesions and the proportion of patients with at least 50% reductions in the total number of basal-cell carcinomas from baseline to end of treatment were greater in treatment group A than in treatment group B.

The per-protocol analysis was consistent with the intention-to-treat analysis, and resulted in greater values for all endpoints, which suggests that outcomes were better in patients who completed of 72 weeks of treatment compared with those who did not. Sensitivity analyses, which excluded patients who had undergone surgical or medical interventions for non-target basal-cell carcinomas after week 32 of treatment, with additional imputation methods (worst case or average) or based on observed data, showed similar outcomes to the primary analysis, indicating consistency of results.

Overall, 53 (23%) of 229 patients discontinued study treatment because of adverse events; this occurred for more patients in treatment group B than in treatment group A (30 *vs* 23). By comparison, in a study of continuous treatment with vismodegib, among 26 patients with basal-cell nevus syndrome, 14 (54%) patients discontinued treatment early because of treatment-emergent adverse events.[13] In the STEVIE global safety study,[11] the largest study so far in patients with basal-cell carcinoma, 380 (31%) of 1215 patients discontinued treatment because of adverse events. The population in the STEVIE study reflects the range of people with advanced basal-cell carcinoma seen in practice, and it included patients with basal-cell nevus syndrome or multiple basal-cell carcinomas if they met the inclusion criteria of locally advanced or metastatic disease.

The second most common reason for discontinuing treatment in the MIKIE study was withdrawal of consent or refusal of treatment, which might have included patients who did not tolerate the treatment, although we did not record specific reasons. Understanding the reasons for treatment discontinuation might be beneficial in future studies.

The safety profile of vismodegib in our intermittent regimens was consistent with profiles in studies of continuous vismodegib dosing schedules.[7,11] The most commonly reported treatment-emergent adverse events in this and other studies were muscle spasms, dysgeusia, and alopecia. Frequency of these adverse

	Treatment group A (n=114)	Treatment group B (n=113)
All	22 (19%)	19 (17%)
Related to study treatment	6 (5%)	2 (2%)
Fatal	2 (2%)*	2 (2%)†

*Includes one death due to pulmonary embolism suspected to be related to study treatment and one death due to pneumonia occurring 70 days after the patient had completed the full treatment period and that was not deemed to be related to study treatment. †Includes one death due to pulmonary embolism and one death due to cardiogenic shock, neither of which were deemed to be related to study treatment.

***Table 5*: Serious treatment-emergent adverse events**

events was similar in our two treatment groups. Although we expected the range of treatment-emergent adverse events in this study to reflect those seen in studies with continuous dosing of vismodegib, intermittent dosing was associated with fewer treatment-emergent adverse events of grade 3 or worse (31% of patients affected in this study *vs* 44% in the STEVIE study[11]). The duration of treatment was longer in the MIKIE study than in the STEVIE study (71·4 weeks *vs* 37·6 weeks). The regimen received in treatment group A was associated with fewer severe treatment-emergent adverse events than that received in treatment group B and, therefore, might improve tolerability in patients who need long-term treatment.

Development of large numbers of basal-cell carcinomas leads to substantial physical and psychological burden for patients. The ideal regimen for long-term treatment with vismodegib should aim to strike a balance between the activity needed to control disease and the potential risk of toxic effects. Our results indicate that interruption of treatment does not compromise the activity of vismodegib. In reality, treatment interruptions are already widely used to manage adverse events related to Hedgehog-pathway inhibitors, and this approach has been included in a consensus recommendation for treatment strategies in patients with advanced basal-cell carcinoma.[15] Use of an intermittent approach is further supported by an exploratory analysis of STEVIE study data into the effects of treatment breaks on the safety and activity profile of vismodegib in patients with locally advanced and metastatic basal-cell carcinoma.[16] The average length of treatment breaks in that study was 22 days, and the median duration of vismodegib treatment lengthened with increasing numbers of breaks, without seeming to compromise activity.

A limitation of the MIKIE trial is that we did not include a treatment group in which patients received continuous treatment with vismodegib, which prevents our activity and safety results being directly comparable with those from previous studies and, more importantly, that no such comparison could be made within this study. Nevertheless, our primary analysis showed that intermittent dosing of vismodegib has sustained activity and was tolerable in patients with multiple basal-cell carcinomas. Although the study was not designed to compare the dosing regimens, the results suggest that both treatment schedules had similar activity and tolerability. In all, our data suggest that intermittent dosing schedules could be a useful strategy for patients with multiple basal-cell carcinomas who need long-term treatment.

Contributors

BD, RK, GR, and DS conceived and designed the study. BD, RK, AH, SF, DZ, BL, J-JG, SP, GR, and DS recruited patients and collected and assembled the data. All authors contributed to the data analysis and interpretation, writing of the paper, and approval of the final draft.

Declaration of interests

BD has received personal fees and grants from Roche. AH has worked as a consultant for Roche. SF has received institutional grants for consultancy, advisory board participation, and speaker bureau activities from Genentech. DZ has received personal fees and non-financial support from Roche. SP has received personal fees from Roche, La Roche Posay, and Novartis, grants and personal fees from Almirall and ISDIN, personal fees and other (trial) support from Leo Pharma, grants from GlaxoSmithKline, and other (trial) support from Merck Sharp & Dohme. FG, DB, and DP are employees of F Hoffmann-La Roche. DS has received grants, personal fees, and fees for advisory board participation, speaker's bureau activities, and fees paid to his institution for study patients from Roche, personal fees from Amgen, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Symsex, and grants and personal fees from Bristol-Myers Squibb. The other authors declare no competing interests.

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