Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Aberrant hedgehog signalling underlies the development of basal-cell carcinomas. We previously reported the interim analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial in patients with the basal-cell nevus (Gorlin) syndrome indicating that the smoothened inhibitor vismodegib reduces basal-cell carcinoma tumour burden and prevents new basal-cell carcinoma growth in patients with basal-cell nevus syndrome. We report the final results of this 36 month trial.

Methods In our multicentre, randomised, double-blind, placebo-controlled, phase 2 trial we enrolled patients aged 35–75 years with basal-cell nevus syndrome with at least ten surgically eligible basal-cell carcinomas at the Children's Hospital Oakland, Columbia University outpatient dermatology clinic (NY, USA) and a private practice outpatient dermatology office in Newport Beach (CA, USA). Patients were assigned to vismodegib or placebo (2:1) according to a randomisation sequence generated by computer code. The primary endpoint of the trial of 41 patients was to compare the effect of oral vismodegib (150 mg/day) versus placebo on the incidence of new surgically eligible basal-cell carcinomas after 3 months of treatment. In the subsequent, open-label phase (n=37) patients continued vismodegib at two sites for as long as month 36 (n=25) and at the third site were monitored up to month 36 (n=12). Additional endpoints for this phase were: whether continuous versus interrupted dosing differentially affected tumour burden; time to reach various levels of reduction in tumour burden; reduction in tumour size in patients who took less than 50% of the expected number of vismodegib tablets; reduction in the number of surgical excisions required per year before, during, and after treatment; and the effect of vismodegib on hedgehog target gene expression. We monitored patients at visits every 3 months for up to 36 months. The primary endpoint was analysed on a modified intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT00957229.

Findings Between Sept 22, 2009, and Jan 24, 2011, 41 patients were monitored for a median of 36 months (IQR 36–36). Patients treated with vismodegib (n=26) had a mean reduced rate of new surgically eligible basal-cell carcinomas compared with patients randomly assigned to placebo (n=15; two [SD 0·12] new surgically eligible basal-cell carcinomas per patient per year *vs* 34 [1·32] new surgically eligible basal-cell carcinomas per patient per year, p<0·0001). In the 11 patients initially assigned to placebo, mean cross over to vismodegib reduced the development of new surgically eligible basal-cell carcinomas compared with placebo (0·4 [SD 0·2] new surgically eligible basal-cell carcinomas per patient per year *vs* 30·0 [7·8] new surgically eligible basal-cell carcinomas per patient per year, p<0·0001). Only three (17%) of 18 patients tolerated vismodegib continuously for the full 36 months. Fewer new surgically eligible basal-cell carcinomas developed in patients receiving vismodegib continuously than in those who interrupted dosing (mean 0·6 [0·72] new surgically eligible basal-cell carcinomas per patient per year *vs* 1·7 [1·8] new surgically eligible basal-cell carcinomas per patient per year, p<0·0001). Treatment-related grade 3–4 adverse events included weight loss of 20% or more (n=6) and muscle cramps (n=2). Two patients died during the course of the trial, one each from laryngeal and metastatic prostate cancer, deemed probably unrelated to drug.

Interpretation Vismodegib reduces basal-cell carcinoma tumour burden in patients with basal-cell nevus syndrome. Adverse events associated with vismodegib frequently led to interruption of treatment, which is followed by basal-cell carcinoma recurrence.

Funding Genentech investigator-initiated trial funding, Clinical and Translational Science Award from the National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Cancer Institute, Damon Runyon Cancer Research Foundation Clinical Investigator Award, Swim across America Foundation, and Michael J Rainen Family Foundation.

Research in context

Evidence before this study

We searched PubMed with the search terms "basal cell nevus syndrome", "Gorlin syndrome", "vismodegib", "hedgehog pathway inhibitor", and "smoothened inhibitor" for peer reviewed papers and abstracts published in the 5 years between April 1, 2011, and June 1, 2016.

Patients with the basal-cell nevus (Gorlin) syndrome have a much higher risk of developing basal-cell carcinomas of the skin due to heritable inactivation of the *PTCH1* gene, which encodes the primary inhibitor of the hedgehog signalling pathway. To the best of our knowledge, vismodegib is the first small molecule inhibitor of the hedgehog signalling pathway to be tested in humans. We assessed the efficacy of this agent against basal-cell carcinomas in patients with basal-cell nevus syndrome in a double-blind, randomised trial. The interim results of which indicated good efficacy but nearly uniform side-effects with consequent drug holidays or even discontinuation. These drug breaks potentially are of concern given that approximately 20% of patients with locally advanced and metastatic basal-cell carcinomas treated with vismodegib develop resistance during the first year of treatment.

Added value of this study

This study is the largest series of patients with basal-cell nevus syndrome who have been treated with vismodegib, and we report here our now more nuanced understanding of the balance between its therapeutic benefits and its adverse effects. Tumours uniformly shrink with vismodegib treatment and even after vismodegib treatment is stopped, there seems to be long-term reduction of the development of new surgically eligible basal-cell carcinomas. But eventually most treated basal-cell carcinomas do recur. Moreover, hair regrowth, initially observed to be complete once the drug is stopped, often is incomplete after longer treatment. Unlike the frequent primary and secondary high resistance rate of advanced basal-cell carcinomas, non-advanced basal-cell carcinomas in these patients remain sensitive to vismodegib with intermittent treatment.

Implications of all the available evidence

Vismodegib can be given safely for as long as 36 months to patients with basal-cell nevus syndrome with excellent control of basal-cell nevus syndrome and without development of resistance but most are unable to take the drug continuously for that duration. When the drug is stopped, the lesions recur, despite apparent clinical and histological disappearance. Restarting of the drug brings repeated clinical benefit but also recurrence of the adverse effects. This study provides important data for the practicality of long-term vismodegib treatment in patients with basal-cell nevus syndrome.

Introduction

Basal-cell carcinomas require aberrant signalling of the hedgehog pathway for growth and maintenance.[1] Basal-cell nevus (Gorlin) syndrome (Online Mendelian Inheritance in Man number, 109400) is a rare heritable disease caused by a constitutive inactivating mutation in *PTCH1*, the gene encoding the primary inhibitor of the hedgehog pathway.[2] Patients with this syndrome might develop hundreds to thousands of basal-cell carcinomas and are at risk for medulloblastomas and other cancers.[2] Vismodegib, the first hedgehog-pathway inhibitor targeting the G-protein coupled receptor smoothened (SMO), was approved by the US Food and Drug Administration in 2012 and by the European Medicines Agency in 2013 for treatment of advanced or metastatic basal-cell carcinomas.[3] Our group previously reported results of our interim analysis of the efficacy of vismodegib in a randomised, double-blind, placebo-controlled, phase 2 trial in patients with basal-cell nevus syndrome, which was subsequently unblinded.[4] We reported that patients treated with vismodegib patients had lower rates of new surgically eligible basal-cell carcinomas and reduced sizes of existing clinically significant basal-cell carcinomas compared with patients treated with the placebo. We report the final efficacy and safety results at the end of the open-label vismodegib period in the full dataset of 41 patients.

Methods

Study design and participants

The study design for this trial has been described previously.[4] We enrolled patients aged 35–75 years, with a clinical diagnosis of basal-cell nevus syndrome,[5] each of whom had a total of at least ten basal-cell carcinomas that were eligible for surgical resection present at study entry or had been removed during the previous 2 years at the Children's Hospital Oakland, Columbia University outpatient dermatology clinic (NY, USA) and a private practice outpatient dermatology office in Newport Beach (CA, USA). Surgically eligible basal-cell carcinomas were defined as those with a diameter of 3 mm or greater on the nose or periorbital skin, 5 mm or greater elsewhere on the face, or 9 mm or greater on the trunk or limbs (excluding the leg below the knees, which was not monitored). We did not test for germline mutations in this study, and no patient had a medulloblastoma, which can sometimes occur as a result of hedgehog mutations. Eligible participants were required to have normal haemopoietic capacity, hepatic function (aspartate aminotransferase and alanine transaminase less than two times the upper limit of normal), renal function, and fasting cholesterol. Women of childbearing potential, even those using contraceptives, were not eligible. Men enrolled in the study as well as their female partners were required to use contraception during the study and for 7 months after the last dose.

Patients had to abstain from application of non-study topical medications to the skin for the duration of the study, including prescription and over the counter preparations, such as topical corticosteroids (other than ≤0·1% triamcinolone applied no more than six times a month), vitamin A derivatives, α-hydroxy acids, fluorouracil or imiquimod. The washout period for topical medications was 6 months before study entry.

The exclusion criteria were patients with: systemic chemotherapy within a year before starting the study medication, Eastern Cooperative Oncology Group performance status of more than 2, uncontrolled systemic disease (including HIV), congestive heart failure, uncontrolled hypocalcaemia, hypomagnesaemia, hypokalaemia, viral hepatitis, or liver cirrhosis.

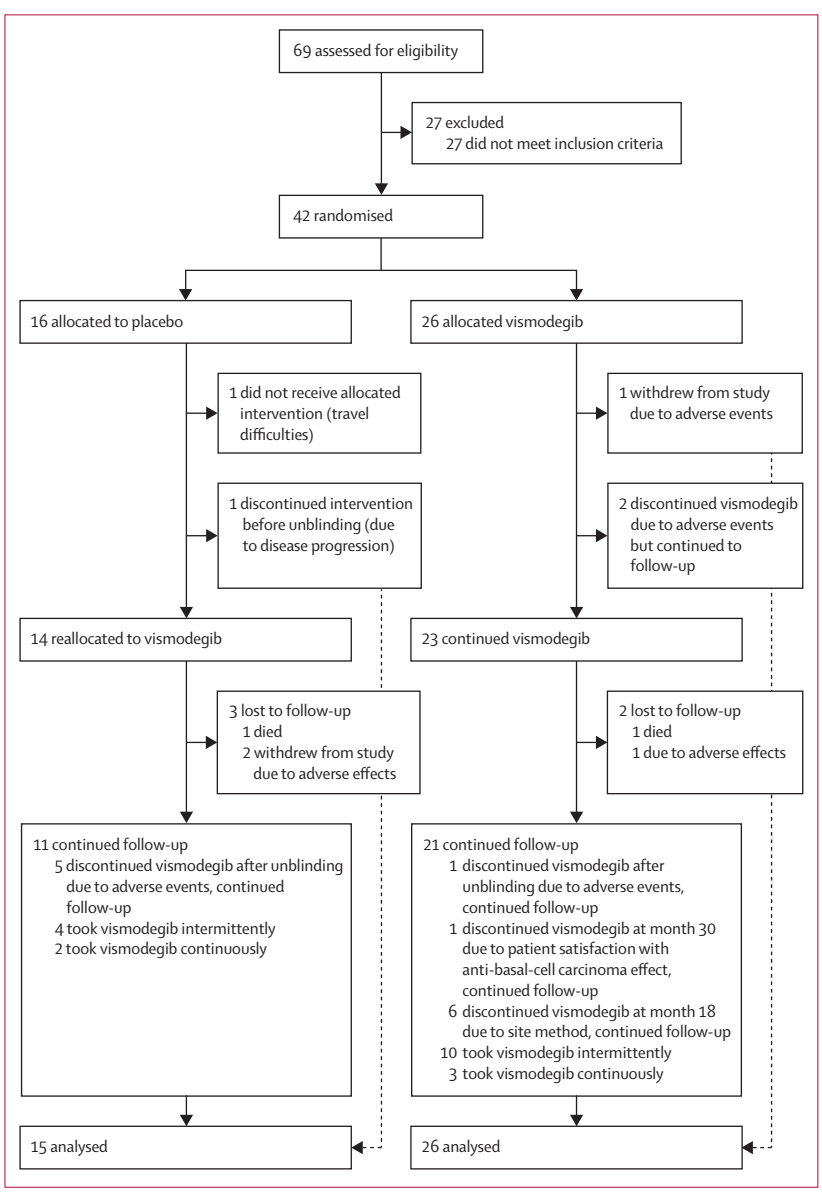

Figure 1: **Trial profile**

We assessed tumour response by examining the skin at study visits and identified basal-cell carcinomas clinically. We used calipers to measure their longest diameter and clinical photos from previous visits to ensure consistency of clinical examination. The number of capsules of vismodegib returned at each study visit was used to measure compliance. Laboratory monitoring for haematology, serum chemistry, and urinalysis was done at each study visit. A mandible MRI was offered to all patients at baseline, when vismodegib was stopped, and at the end of the participation. However, only a subset of patients opted to have imaging, and these results have been previously published.[6] We used the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) to characterise adverse events. Patients gave written informed consent and the study was approved by the institutional review boards of the Children's Hospital Oakland Research Institute (CA, USA) and Columbia University Medical Centre (NY, USA).

Randomisation and masking

The study investigators confirmed the eligibility of participants according to stated inclusion and exclusion criteria. At baseline, patients were randomly assigned (2:1) to treatment with vismodegib versus placebo according to a computer code-generated randomisation sequence. Participants were not stratified and randomisation was done separately for patients enrolled in the California and Columbia Centres to reduce the likelihood that all patients at any one centre would be assigned (randomly) to the same treatment group.

Unblinded information about drug assignment was known only to the biostatistician, the research pharmacists who prepared the labelling of the bottles of capsules, and the members of the Data Safety Monitoring Board. Investigators, patients, and other non-pharmacy study personnel maintained their blinded status.

Procedures

Each patient received the study drug (oral vismodegib; Genentech, South San Francisco, CA, USA) at a dose of 150 mg daily for a maximum of 18 months or until the occurrence of intolerable toxic effects or clinical worsening of disease (defined as >60 new surgically eligible basal-cell carcinomas or doubling of the cumulative longest diameter of existing or new surgically eligible basal-cell carcinomas). Treatment with vismodegib or placebo could be interrupted because of toxicity or for a planned surgical procedure. During the trial, patients could elect to undergo surgical removal at the discretion of their primary skin care physician. The number of basal-cell carcinomas removed during the trial was recorded during study visits. We monitored patients for a year after study completion. At the end of the trial, patients were also questioned by telephone regarding the number of

basal-cell carcinoma surgeries they underwent before and after vismodegib treatment.

At the planned interim analysis in December, 2010, the Data and Safety Monitoring Board recommended ending the placebo treatment because of significant differences in efficacy favouring the vismodegib group. The data cutoff date was Feb 17, 2011, when the institutional review board of Children's Hospital Oakland Research Institute approved the recommendation. The study was unblinded, and on March 1, 2011, those assigned to placebo were offered open-label vismodegib. The originally planned 18 month period of monitoring was extended to offer all patients the opportunity to continue participation in the trial for up to 36 months and to be monitored during that time irrespective of whether or not they received the drug. At all sites, patients were monitored at every 3 months for up to 36 months. Patients at the California sites were offered the opportunity to continue vismodegib until month 36 of the study and were permitted to interrupt drug treatment due to adverse events, if desired. Patients at the Columbia University sites were offered the opportunity to receive vismodegib for a maximum of 18 months and were followed up for the remainder of the 36 month study period.

	Vismodegib (n=26)	Placebo (n=15)
Age (years)	54 (8)	53 (8)
Sex		
Male	18 (69%)	9 (60%)
Female	8 (31%)	6 (40%)
Weight at baseline (kg)	100 (24)	100 (29)
Number of surgically eligible basal-cell carcinomas at baseline	44 (41)	37 (50)
Last visit in allocated intervention (months)	9 (5)	8 (5)
Last visit in study (months)*	33 (7)	33 (7)
Total number of months of vismodegib (months)*	21 (9)	16 (7)

Data are mean (SD) or n (%).*Data in the last two rows are the per protocol population; one patient assigned to placebo was removed from the study before receiving the first dose of vismodegib therefore n=14 for the placebo group.

Table 1: **Baseline characteristics of 41 patients with basal-cell nevus syndrome**

Outcomes

The primary endpoint of the trial was the reduction in the incidence of new surgically eligible basal-cell carcinomas after 3 months in the vismodegib versus placebo groups, an endpoint that was met at the interim analysis. However, at the time of the interim analysis not all patients had completed 18 months on the study. Secondary endpoints were the reduction in size (cumulative diameter) of existing surgically eligible basal-cell carcinomas, duration of efficacy in basal-cell carcinomas prevention after drug discontinuation, and development of adverse events related to vismodegib. In the open-label phase, additional exploratory endpoints were the time to reach various levels of reduction in tumour burden (eg, time taken to reach 50% reduction in cumulative diameter of existing surgically eligible basal-cell carcinomas), reduction in the size of all surgically eligible basal-cell carcinomas in patients who took less than 50% of the expected number of vismodegib tablets throughout the study versus in patients ingesting more than 80%, the early effect of vismodegib on hedgehog target gene expression in basal-cell carcinomas, and reduction in the number of surgical excisions required per year before, during, and after vismodegib treatment.

The full method used to assess drug-induced inhibition of hedgehog signalling before and after 1 month of

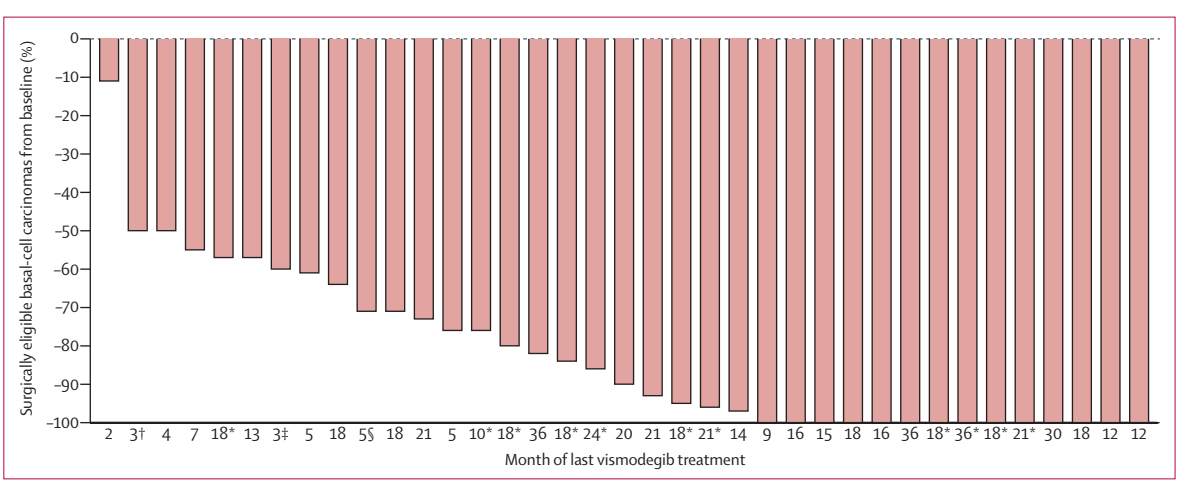

Figure 2: **Waterfall plot of change in size of surgically eligible basal-cell carcinomas from baseline to the time of last vismodegib treatment (n=37)**
The sum is shown of longest diameter of all surgically eligible basal-cell carcinomas from baseline for each patient that received vismodegib, at the time of the study month at last visit of vismodegib treatment. *Ingested continuous vismodegib (with less than a 1 month break). Four patients were excluded from the plot due to surgical excision of existing basal-cell carcinomas during placebo period (n=2), reclassification of baseline surgically eligible basal-cell carcinomas as non-basal-cell carcinoma (n=1), and removal from trial during placebo period due to basal-cell carcinoma progression (n=1). †Patient A. ‡Patient B. §Patient C.

	Placebo (n=15)		Vismodegib (n=40)				p value			
	Grade 1–2*	Grade 3*	Grade 1–2*	Grade 3*	Grade 4*	Death*	Grade 1–2	Grade 3	Grade 4	Death
Hair loss	1 (7%)	0 (0%)	40 (100%)	0 (0%)	0 (0%)	0 (0%)	<0·0001	..	..	..
Muscle cramps	1 (7%)	0 (0%)	40 (100%)	2 (8%)	0 (0%)	0 (0%)	<0·0001	1·00	..	..
Dysgeusia	1 (7%)	0 (0%)	37 (93%)	0 (0%)	0 (0%)	0 (0%)	<0·0001	..	..	..
Gastrointestinal upset†	2 (13%)	0 (0%)	26 (65%)	0 (0%)	0 (0%)	0 (0%)	<0·0001	..	..	..
Weight loss‡	1 (7%)	0 (0%)	25 (63%)	6 (15%)§	0 (0%)	0 (0%)	<0·0001	0·17	..	..
Fatigue	0 (0%)	0 (0%)	19 (48%)	0 (0%)	0 (0%)	0 (0%)	<0·0001	..	..	..
Common cold	3 (20%)	0 (0%)	8 (20%)	0 (0%)	0 (0%)	0 (0%)	..	..	..	..
Acne	2 (13%)	0 (0%)	7 (18%)	0 (0%)	0 (0%)	0 (0%)	1·00	..	..	..
Runny nose	0 (0%)	0 (0%)	7 (18%)	0 (0%)	0 (0%)	0 (0%)	0·17	..	..	..
Rash	0 (0%)	0 (0%)	5 (13%)	0 (0%)	0 (0%)	0 (0%)	0·31	..	..	..
Dizziness	0 (0%)	0 (0%)	4 (10%)	0 (0%)	0 (0%)	0 (0%)	0·57	..	..	..
Nausea	1 (7%)	0 (0%)	4 (10%)	0 (0%)	0 (0%)	0 (0%)	1·00	..	..	..
Pneumonia	0 (0%)	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	..	1·00	..	..
Reactions to antibiotic¶	0 (0%)	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	..	1·00	..	..
Chest pain	0 (0%)	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	..	1·00	..	..
Atrial flutter	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	..	1·00	..	..
Colitis	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	..	1·00	..	..
Oesophagitis	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	..	1·00	..	..
Hip replacement surgery	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	..	1·00	..	..
Knee replacement surgery	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	..	1·00	..	..
Mesenteric cyst	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	..	1·00	..	..
Cardiac stent for blocked artery	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	..	0·27	..	..
Hysterectomy	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	..	0·27	..	..
Suicide attempt‖	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	..	..	1·00	..
Death due to recurrent prostate cancer	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	..	..	..	1·00
Death due to laryngeal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	..	..	..	1·00

Data are n (%). Grade 1 and 2 events are listed only if investigators considered them to be related to vismodegib treatment. All other graded events are listed. The highest grade of event is reported for each patient. *Some adverse events might be duplicated in both treatment groups because all patients crossed to the vismodegib group. †Gastrointestinal upset includes all notable changes in bowel movements, including diarrhoea, and constipation. ‡From baseline, grade 1 weight loss is 5% to <10%, grade 2 is 10% to <20%, and grade 3 is ≥20%. §One patient had only 2 months of vismodegib and had grade 3 weight loss by month 27 after joining intentional weight loss efforts. ¶Reactions to antibiotics include ciprofloxacin and Bactrim. ‖This patient had severe depression and multiple suicide attempts before treatment with vismodegib.

Table 2: **Adverse events**

treatment with vismodegib has been previously described.[4] We report the change in mRNA expression of *GLI1* (a hedgehog target gene) from baseline to 5–7 days of vismodegib treatment.

Statistical analysis

The full statistical analysis for this study has been described previously.[4] Briefly, we calculated that with a 2:1 randomisation, we would need to enrol 20 patients on vismodegib and ten patients on placebo to reach statistical significance assuming five new surgically eligible basal-cell carcinomas in drug (SD 3) versus ten new surgically eligible basal-cell carcinomas in placebo (SD 5) during the study, with a significance level of 0·05 and power of 80% (Stata SE, version 12.1). We enrolled a total of 41 patients to account for a 20% dropout and for potential per-protocol analyses. All the analyses for the primary outcome were intention to treat with the generalised linear model (SAS, version 9.3) and were prespecified before the data were unblinded and included data from all patients who were randomly assigned to a study group. We included the clinic site and number of surgically eligible basal-cell carcinomas at baseline as covariates to account for variability among patients. The primary modified intention-to-treat analysis was not planned and powered for statistical significance, but was planned as a proof of concept study to show clinical significance only. No imputation of missing data in the primary intention-to-treat analysis was done, because it was assumed that any data are missing at random and because the generalised linear model takes into account the follow-up time contributed by any patient. The secondary exploratory outcomes were analysed by per-protocol with two-sided *t* tests (GraphPad Prism, version 7). Additionally, we plotted the time to first vismodegib drug break, time to basal-cell carcinoma shrinkage and recurrence after discontinuing vismodegib for illustration purposes only; they were not formally analysed. This trial is registered with ClinicalTrials.gov, number NCT00957229.

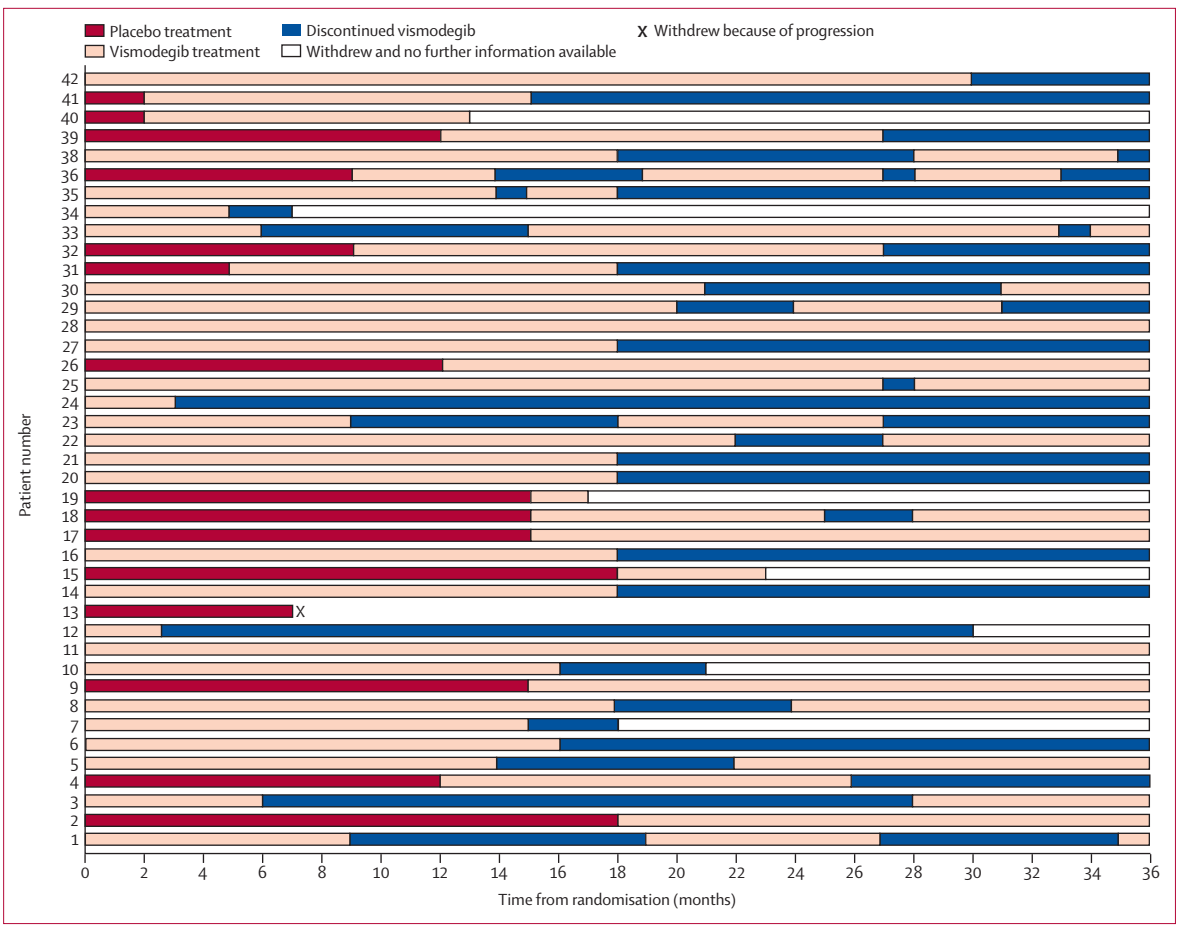

Figure 3: **Treatment timelines plotted for individual patients throughout the study (n=41)**
One patient was excluded as they did not receive the allocated intervention and were removed from the study.

Role of the funding source

The sponsors had no role in study design, collection, analysis or interpretation of the data, or writing of the report. All authors had full access to the data in the study and contributed to the writing of this manuscript. The corresponding author (EHE) had full access to all of the data and the final responsibility to submit for publication.

Results

In the prospective, randomised, double-blind, placebo-controlled, multicentre, phase 2 trial, we enrolled 42 eligible patients with basal-cell nevus syndrome at three clinical centres (two in California and one in New York, USA) from Sept 22, 2009, to Jan 24, 2011 (figure 1). One patient withdrew from the study before receiving the allocated intervention. Baseline characteristics were similar between vismodegib and placebo groups (table 1). At the end of the double-blind phase of the trial, 23 patients continued vismodegib and 14 patients receiving placebo switched to vismodegib (open label). Three (12%) of 26 patients originally assigned to vismodegib treatment discontinued drug before unblinding because of adverse events (patients A, B, and C; figure 2), and of these, two patients continued to attend follow-up visits. One patient in the placebo group was removed from the trial before unblinding due to disease progression. The median time of monitoring for the 41 patients who received at least one dose of the allocated intervention was 36 months (IQR 36–36; mean 33 months, SD 8). Of these 41 patients, 34 patients (83%) continued to attend follow-up visits for the full 36 month study period.

Over 36 months, we followed up more than 2000 surgically eligible basal-cell carcinomas present at baseline, and 775 new surgically eligible basal-cell carcinomas. The results of the full analysis at the end of the trial at 36 months strongly resemble those at the interim analysis.[4] All 41 treated patients completed at least 3 months of follow-up visits and had data for the primary endpoint (reduction in the rate of new surgically eligible basal-cell carcinomas) after 3 months of receiving study drug (figure 1). All patients who received vismodegib experienced shrinkage in their tumours (figure 2).

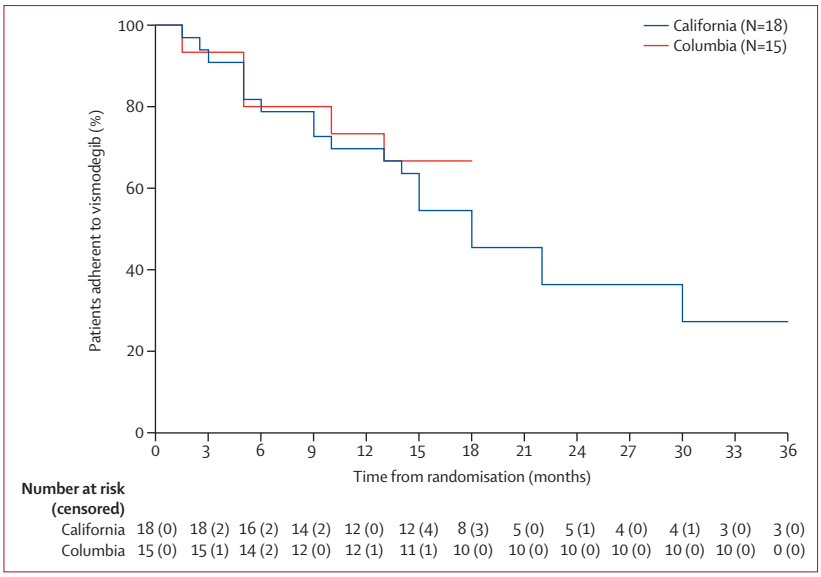

Figure 4: **Adherence to vismodegib over 36 months**
Only the 18 patients from the 25 patients treated at the California sites originally allocated to the vismodegib group were offered vismodegib treatment for an additional 18 months (up to month 36). Patients at Columbia were offered the opportunity to receive vismodegib for a maximum of 18 months and were followed up for the remainder of the 36 month study period, therefore their data cutoff was at month 18.

During the double-blind, randomised phase of the trial, patients treated with vismodegib (n=26) had a reduced mean rate of new surgically eligible basal-cell carcinomas compared with patients treated with placebo (n=15; two [SD 0·12] new surgically eligible basal-cell carcinomas per patient per year *vs* 34 [1·32] new surgically eligible basal-cell carcinomas per patient per year, p<0·0001). The 11 patients (excluding the two patients who were excluded due to surgical excision of existing basal-cell carcinomas during placebo period and the one patient who had a short treatment period with vismodegib of 2 months, which prevented evaluation) who crossed over to vismodegib after unblinding developed fewer new surgically eligible basal-cell carcinomas with vismodegib treatment as compared with placebo treatment (0·4 [SD 0·2] new surgically eligible basal-cell carcinomas per patient per year *vs* 30·0 [7·8] new surgically eligible basal-cell carcinomas per patient per year, p<0·0001). Vismodegib also reduced the size of the existing carcinomas, expressed as the sum of cumulative diameters over an 18 month period (–60 mm for vismodegib *vs* 55 mm for placebo, p<0·0001 or –56% for vismodegib from baseline [n=26] *vs* 13% for placebo [n=15], p<0·0001). The incidence of new surgically eligible basal-cell carcinomas after stopping vismodegib was analysed in an exploratory analysis of the patients who crossed over to vismodegib and were followed up for at least 6 months after stopping vismodegib (n=5). The remaining six patients who switched from placebo to vismodegib were not included in this analysis because they did not have a substantial period off drug to assess new surgically eligible basal-cell carcinoma development.

See Online for appendix

Vismodegib seemed to reduce the frequency of new surgically eligible basal-cell carcinomas even after stopping treatment in these patients. These five patients were given placebo for a mean of 7·4 months (SD 2·3) during which they developed new surgically eligible basal-cell carcinomas at a mean rate of 1·7 (1·5) per month. After receiving vismodegib for a mean of 13·8 months (SD 6·8) and then discontinuing vismodegib for a mean of 11·8 months (7·9), the rate of development of new surgically eligible basal-cell carcinomas while not taking vismodegib was mean 0·06 per month (0·12; rate of development of these carcinomas in the placebo group compared with the rate after discontinuation of vismodegib, p=0·060).

Most patients (31 [74%] of 42 patients) needed interruptions in vismodegib treatment due to adverse events (table 2, figure 3). The continuous adherence of patients scheduled for 36 months of treatment or 18 months of treatment is shown in figure 4. Only three (17%) of 18 patients tolerated vismodegib continuously for the full 36 months. Due to the high rate of drug interruption, we examined whether the number of tablets consumed during the scheduled period for vismodegib treatment would affect the rate of new surgically eligible basal-cell carcinomas after discontinuation. We compared patients who were characterised as very compliant (ingesting at least 80% of the prescribed vismodegib pills) with patients who were very incompliant (ingesting less than 50% of pills). Very compliant patients (n=16) developed 0·6 (SD 0·72) new surgically eligible basal-cell carcinomas per patient per year versus 1·7 (1·8) new surgically eligible basal-cell carcinomas per patient per year for very incompliant patients (n=14; p<0·0001). The remaining 11 of 41 patients were not included in this analysis as they did not receive vismodegib (n=1), received fewer than 2 months of vismodegib (n=3), took vismodegib continuously for only a short period (n=2), ingested 50–79% pills (n=3), had multiple excisions (n=1), and had some lesions reclassified as not basal-cell carcinomas (n=1). We noted that new surgically eligible basal-cell carcinomas recurred during drug breaks but did shrink in size and number after the patient restarted vismodegib (appendix p 1). Those patients treated with vismodegib continuously for longer periods of time seemed to have a longer duration of benefit after stopping the drug. In patients who took vismodegib continuously for at least 15 months (n=10), the anti-basal-cell carcinoma effect was maintained (ie, there was no return to baseline tumour burden) for 18 months after discontinuing the drug (figure 5A). Comparing the effect of long-term vismodegib treatment to short-term treatment on tumour burden recurrence after discontinuing the drug, 22 (54%) of 41 patients discontinued vismodegib for 6 months or longer, during which we were able to analyse the percentage of tumour burden recurrence from baseline (figure 5B). Of these 22 patients, 11 (50%) had a recurrence of 50% or more of

baseline tumour burden over a median of 7·0 months (IQR 6·0–9·0); three of 11 patients had a 90% recurrence of baseline basal-cell carcinoma burden over a median of 21·0 months (IQR 16·5–25·5); and only one of 11 reached baseline tumour burden after a first drug interruption of 12 months and then, 8 months later, a second drug interruption of 7 months.

The median times for patients (n=36, excluding the one patient who had a treatment period of 2 months preventing evaluation) to have tumour shrinkage of existing surgically eligible basal-cell carcinomas of 50% was 3 months (IQR 2–5) , of 90% was 7 months (4–14), and of 100% was 15 months (9–15). 19 patients had 100% shrinkage of surgically eligible basal-cell carcinomas by month 27 (figure 6). 23 patients reported fewer basal-cell carcinoma surgeries by physician discretion during vismodegib treatment (p<0·0001; table 3) and for a mean of 14 months (SD 7) follow-up after stopping the drug (p=0·0010; table 3). Basal-cell carcinoma excisions while taking vismodegib occurred mostly during the first 3 months of treatment, although in one case the primary skin care physician opted to remove even small vismodegib-responsive basal-cell carcinomas after 3 months of treatment. Of the 23 patients who responded to the questionnaire, 18 (78%) preferred treatment with vismodegib to surgery, and 17 (74%) continued vismodegib after completing the trial, despite the adverse effects. In general, patients' reasons for restarting vismodegib were related to the recurrence of basal-cell carcinomas although most did not wait until their tumour burden returned to baseline levels.

During the study, 19 (76%) of the 25 patients at the California sites chose to discontinue vismodegib temporarily or permanently due to adverse events (table 4). Data were not collected with reasons for interruption at the Columbia sites. Most adverse events were mild or moderate in severity and were similar to those described previously for treatment with vismodegib.[4] Muscle cramps and dysgeusia occurred within 2 months of vismodegib initiation and they resolved in all patients within 1·5 months of drug discontinuation. Of seven patients from all three sites who were treated with continuous vismodegib for 16–18 months followed by drug discontinuation for at least 18 months, it took a median of 12 months for them to lose 50% of their scalp and (in men) facial hair. More complete alopecia during vismodegib treatment was more frequently associated with no restoration of hair growth to baseline. Only two (30%) of the seven patients had hair growth return to baseline during the 18 month follow-up. To our knowledge, no patient developed cutaneous squamous cell carcinoma, which has been previously reported with vismodegib treatment during the trial or during the 12 month follow-up after completion of the trial.[7]

Two deaths occurred during the trial probably unrelated to drug. One patient died 9 months after discontinuing vismodegib due to metastatic supraglottic laryngeal squamous cell carcinoma, which was diagnosed while on the study, and following diagnoses the patient was no longer given vismodegib. The second patient was originally randomly assigned to vismodegib, and had previously had stage T3 prostate cancer which had been controlled. After 16 months of continuous vismodegib treatment the patient developed clinically apparent, hormone resistant, prostate cancer with bone metastases at which time vismodegib treatment was stopped; the patient died 25 months later.

Residual microscopic basal-cell carcinoma was present in all 20 of the biopsy specimens obtained from six patients with basal-cell carcinomas that were clinically

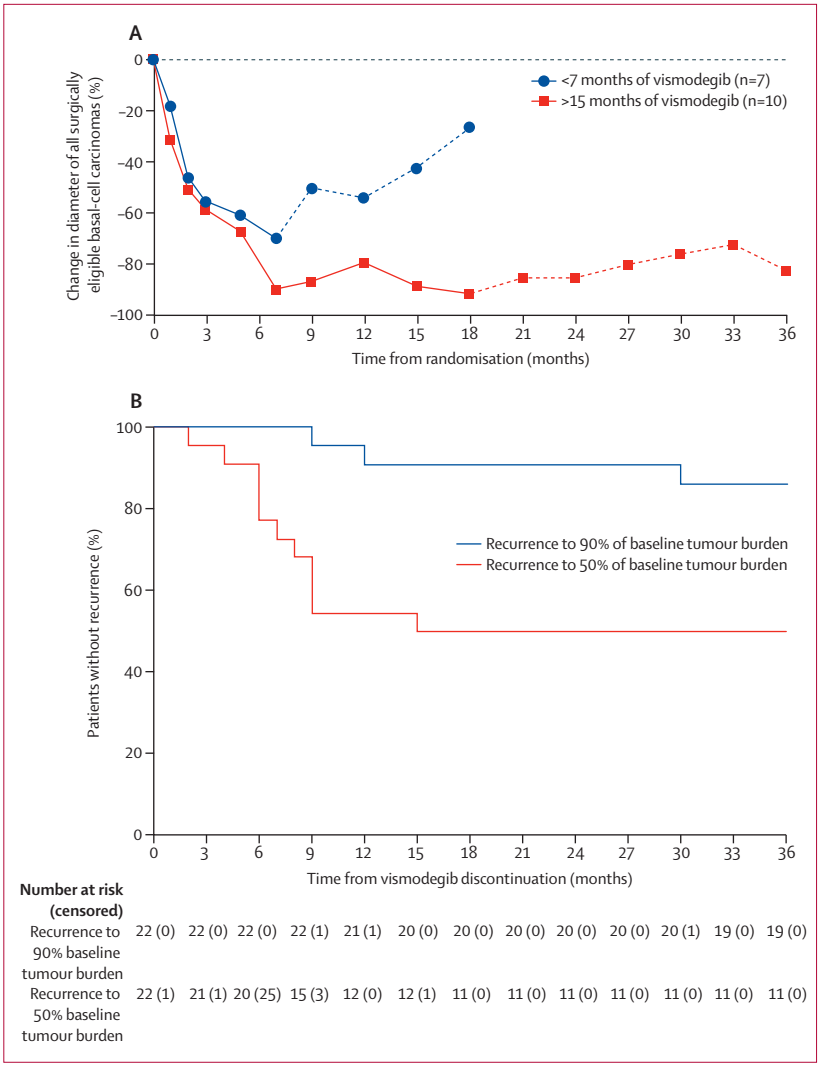

Figure 5: **Recurrence of basal-cell carcinoma burden after drug discontinuation**
(A) Median percent change in diameter of all surgically eligible basal-cell carcinomas. Solid lines represent time on vismodegib; dashed lines represent time off vismodegib. Only 17 patients are included: patients treated with vismodegib continuously for more than 15 months with at least 6 months of follow-up off drug (n=10) and patients who received less than 7 months of vismodegib with at least 6 months of follow-up off drug (n=7). (B) Time to 50% and 90% recurrence of baseline tumour burden after discontinuing vismodegib. 22 of 41 patients are included as only 22 completed an initial 3 months on drug and then discontinued vismodegib for 6 months or longer, during which we were able to analyse the percentage of tumour burden recurrence from baseline.

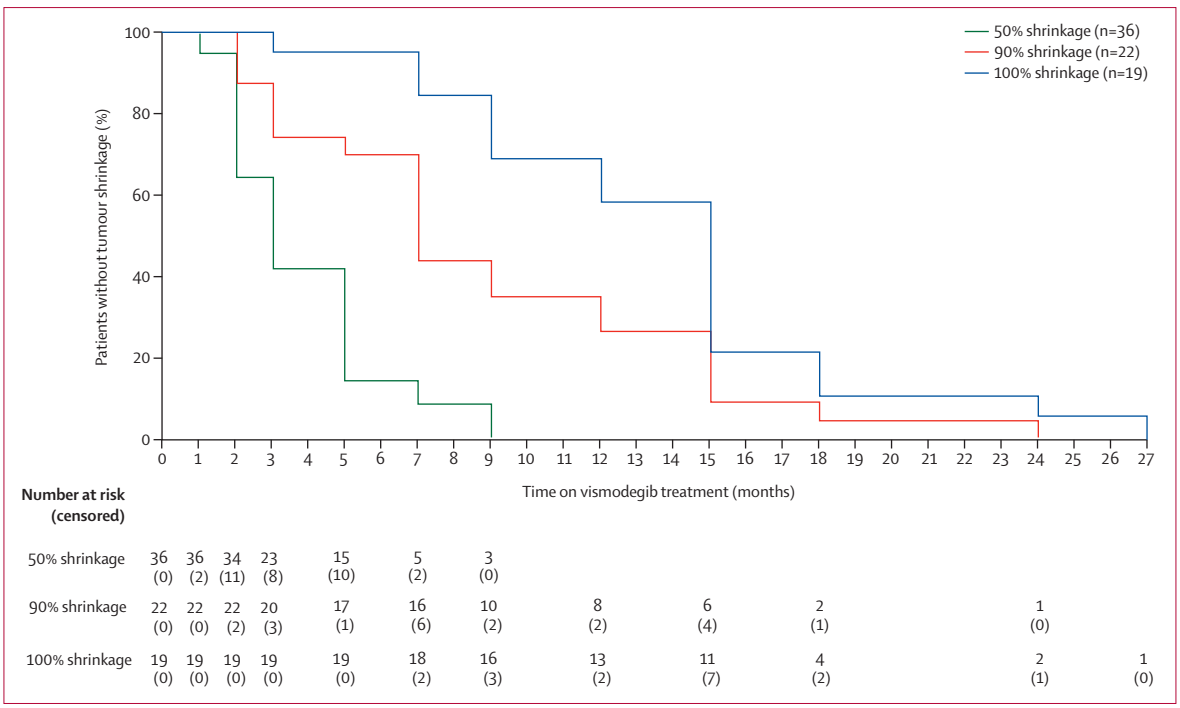

Figure 6: **Time to 50%, 90%, and 100% shrinkage in the diameter of existing surgically eligible basal-cell carcinomas**
Five patients were not assessable due to surgical excision of existing basal-cell carcinomas during placebo period (n=2), reclassification of tumours as not basal-cell carcinoma (n=1), short treatment period with vismodegib (2 months) preventing evaluation (n=1), and removal from trial due to tumour progression (n=1).

raised (papules or plaques) in patients treated with vismodegib for 5–7 days. Vismodegib treatment was also associated with a 50% decrease (p=0·050) in *GLI1* messenger RNA in biopsies from these six patients (appendix p 2) and decreased Ki67 expression, a marker of proliferation (appendix p 2). Vismodegib was also associated with an increase in the apoptotic marker cleaved caspase 3 but this did not achieve statistical significance (appendix p 2).

We identified only two vismodegib-resistant basal-cell carcinomas (ie, tumours that continued to grow or did not shrink while the patient was taking vismodegib) on our study in two separate patients. Patients with these resistant carcinomas also had multiple other carcinomas which all responded to vismodegib. One resistant carcinoma eventually required excision and histology analysis confirmed that it was a basal-cell carcinoma; sequencing did not reveal any mutations in *SMO*, a member of the hedgehog pathway, mutations in which were suspected to underlie resistance. A biopsy of the other resistant tumour confirmed persistent basal-cell carcinoma and sequencing identified a Val321Met SMO mutation.

Discussion

This study confirms the efficacy of vismodegib in reducing tumour burden of existing and new surgically eligible basal-cell carcinomas in patients with basal-cell nevus syndrome. The results of the final analysis are similar to those of the interim report,[4] showing that vismodegib treatment can, in some patients, induce complete clinical resolution of basal-cell carcinomas.

However, only three (17%) of 18 patients scheduled for a 36 month treatment course and only five (13%) of all 40 patients in the trial overall that received vismodegib were to tolerate treatment without a treatment break owing to adverse events. This finding is challenging because fewer new surgically eligible basal-cell carcinomas developed in patients receiving vismodegib continuously than in those who interrupted dosing, and most surgically eligible basal-cell carcinomas recur after discontinuation of the drug. Importantly, the duration of benefit after stopping vismodegib might be proportional to the duration of drug ingestion and to protocol compliance during treatment. Additionally, our data show that the rate of new surgically eligible basal-cell carcinomas was reduced even after drug discontinuation. Finally, resistance to vismodegib was rare in our trial.

We found that patients receiving more than 80% of the prescribed number of vismodegib tablets developed fewer new surgically eligible basal-cell carcinomas than did those who took less than 50% of the expected number of tablets. We also noted that 50% of patients required at least 7 months of vismodegib treatment to reduce their tumour burden by 90%. A randomised, double-blind, multicentre study (NCT01815840)[8] is ongoing to assess the efficacy and safety of two long-term intermittent vismodegib dosing regimens in patients with multiple

basal-cell carcinomas. One group (A) was treated with vismodegib for 150 mg per day for 12 weeks, then three courses of placebo for 8 weeks alternating with vismodegib for 12 weeks, and the other group (B) was treated with vismodegib 150 mg day for 24 weeks, then three courses of placebo for 8 weeks alternating with vismodegib for 8 weeks. At the primary analysis cutoff, they concluded that both treatment regimens were efficacious, with treatment interruptions not seeming to affect efficacy in either regimen.

The adverse events from vismodegib included mostly grade 1–2 dysgeusia, muscle cramps, hair loss, and weight loss.[9] However, unlike the completely reversible hair loss we described with short-term treatment,[10] we found that only 30% of patients who completed 16–18 months of vismodegib had hair growth return to baseline during the ensuing 18 month observation period. Despite the adverse events leading to frequent temporary or permanent discontinuation of vismodegib, 78% of patients preferred vismodegib to surgery, perhaps because of the fewer surgical excisions reported during treatment and for a mean of 14 months after discontinuing vismodegib compared with before starting the trial. Additionally, we previously reported that vismodegib reduced the mean longest diameter of keratocystic odontogenic tumours in a subset of these patients by 1·0 cm (95% CI 0·03–1·94; p=0·02) or 50% from baseline.[6] These tumours affect more than 65% of patients with basal-cell nevus syndrome and can cause facial disfigurement. We noted no enlargement of existing or new keratocystic odontogenic tumour development during vismodegib treatment, suggesting that vismodegib might offer an alternative to surgical therapy in this setting.

Two deaths occurred during vismodegib treatment—one each from laryngeal and metastatic prostate cancer. We noted one previous report of a patient with basal-cell nevus syndrome developing squamous cell carcinoma of the larynx.[11] Two patients with locally advanced or metastatic basal-cell carcinoma treated with another hedgehog inhibitor (sonidegib) developed new prostate cancers during treatment, one of whom had basal-cell nevus syndrome (Dummer R, University of Zurich, Zurich, Switzerland, personal communication).[12,13] Over-expression of hedgehog signalling has been noted in prostate cancer in both animal models and human samples; there are emerging clinical data suggesting that inhibition of the hedgehog pathway might be effective in the treatment of recurrent and metastatic prostate cancer;[14] and there are five ongoing clinical trials assessing the usefulness of hedgehog inhibitors in prostate cancer (NCT02111187, NCT01163084, NCT01787331, NCT02115828, and NCT02182622). Despite promising preclinical results, efforts to use hedgehog-pathway inhibitors for clinical benefit in human solid cancers such as ovarian cancer,[15] colorectal cancer,[16] and pancreatic cancer[17] have been disappointing.

	Results
Number of surgeries* per patient (per year) before vismodegib treatment†	28·0 (19·6)
Number of surgeries per patient (per year) during vismodegib	0·5 (0·5)
Number of surgeries per patient (per year) after discontinuing trial while off vismodegib (n=15)†‡	4·9 (6·3)
Number of months on vismodegib	16·3 (11·4)

Data are mean (SD).*Surgery indicates the removal of a single basal-cell carcinoma, which includes removal by simple excision or microscopically controlled surgery. Data include only patients for comparison who were eventually treated with vismodegib, ie, the original 26 patients randomly assigned to vismodegib and 14 patients from the placebo group that received vismodegib after unblinding (n=40). †Data were only available in 23 patients who answered the telephone questionnaire. ‡After a mean of 14 months (SD 7) of discontinuing vismodegib.

Table 3: **Number of surgeries before and after vismodegib treatment**

	Temporary discontinuation (n=11)	Permanent discontinuation (n=8)
Combination of adverse events	3 (12%)	2 (8%)
Muscle cramps	2 (8%)	2 (8%)
Gastrointestinal upset*	1 (4%)	1 (4%)
Dizziness	1 (4%)	0 (0%)
Fatigue	1 (4%)	0 (0%)
Hair loss	1 (4%)	0 (0%)
Weight loss	1 (4%)	0 (0%)
Suicidal ideation	0 (0%)	1 (4%)†
Allergic reaction to antibiotics	0 (0%)	1 (4%)
Before non-basal-cell carcinoma surgical procedure	1 (4%)	0 (0%)
Patient satisfied with the anti-basal-cell carcinoma effect after 30 months and deemed no further treatment necessary	0 (0%)	1 (4%)

Data are n (%). Four patients received vismodegib without interruption and two patients died during the trial and are included in the above table. Reasons for discontinuation of drug were not available for patients at the Columbia site. *Gastrointestinal upset includes all notable changes in bowel movements, including diarrhoea and constipation. †This patient had severe depression and multiple suicide attempts before treatment of vismodegib.

Table 4: **Reasons for temporary or permanent discontinuation of vismodegib in 19 of 25 patients at the California sites**

Because the onset of the laryngeal and prostate cancer observed in patients in our study seemed to have preceded treatment with the drug it seems unlikely that vismodegib caused the tumours, however, it is possible that vismodegib treatment could have hastened their progression. A study[18] investigating the role of hedgehog signalling in the formation of murine pancreatic ductal adenocarcinoma and its precursor lesion, pancreatic intraepithelial neoplasia, found that hedgehog inhibition accelerated the progression of the oncogenic KRAS-driven portion of this disease. Specifically, hedgehog inhibition affected the balance between epithelial and stromal elements, suppressing stromal desmoplasia but accelerating the growth of pancreatic intraepithelial neoplasia. Similar results were noted in studies investigating hedgehog-pathway inhibition in benign

prostatic hyperplasia[19] and bladder cancer,[20] with studies showing that hedgehog inhibition leads to accelerated disease progression and decreased survival in bladder cancer.[20] Thus, further study is needed to determine whether hedgehog inhibitors might contribute to the development or progression of prostate and laryngeal carcinoma through stromal–epithelial interaction.

Previous studies have shown that the majority (75%) of histologically examined basal-cell carcinomas in basal-cell nevus syndrome are of the nodular subtype, with the next most common subtype being superficial (13%).[21] One limitation of our study is that we did not biopsy all tumours, however, we saw no difference in response to vismodegib based on clinical basal-cell carcinoma subtype, other than the development of secondary acquired resistance in one locally advanced basal-cell carcinoma. Approximately 20% of patients with locally advanced and metastatic basal-cell carcinomas treated with vismodegib develop resistance during the first year of treatment.[22] Recent studies have noted the presence of *SMO* mutations in 15–33% of untreated advanced basal-cell carcinomas, and this proportion increases to 69–77% in SMO-inhibitor resistant tumours.[23,24] By contrast, we found that resistance to hedgehog inhibitors is less frequent in these smaller, basal-cell nevus syndrome-related basal-cell carcinomas than has been reported in sporadic advanced basal-cell carcinomas. Only one of the basal-cell carcinomas monitored in this study was locally advanced at the time of enrolment. Of the two tumours that progressed while receiving vismodegib, one was locally advanced but did not have any identifiable *SMO* mutations: the other was not locally advanced and responded initially to vismodegib but then became resistant and was found then to have a Val321Met SMO mutation. This mutation lies at the interface between the ligand-binding pocket and the autoinhibitory loops of SMO and confers constitutive activation and drug resistance.[23] It is unclear why we did not observe more acquired drug resistance in this study. One possibility is that our patients did not have any advanced basal-cell carcinomas, in which most cases of resistance occur.[22] This suggests that vismodegib resistance typically is limited to locally advanced or more aggressive basal-cell carcinomas. To our knowledge, these data are the first to document the scarcity of resistance to long-term vismodegib in non-locally advanced basal-cell carcinomas. We also found no evidence of primary drug resistance in any of our patients. This could be explained by the frequent absence of somatic *SMO* mutations in basal-cell carcinomas of patients with basal-cell nevus syndrome compared with sporadic basal-cell carcinomas.[25] Additionally, intermittent dosing did not drive drug resistance, an event that often occurs in other malignancies after treatment interruption.[26,27] Thus, when vismodegib was restarted to treat basal-cell carcinomas that had recurred during the drug break, the recurrent basal-cell carcinomas responded just as they did to the initial course of treatment. One potential explanation for this disparity is that unlike many other human malignancies, which are capable of engaging other pathways to circumvent targeted inhibitors, basal-cell carcinomas seem to be largely, if not exclusively, dependent on the hedgehog pathway.[23,24]

Overall, our findings confirm the efficacy of vismodegib in preventing and treating basal-cell carcinomas in patients with basal-cell nevus syndrome. Unfortunately, despite their efficacy, inhibitors of hedgehog signalling are associated with adverse events which necessitate treatment interruption in most patients, resulting in tumour recurrence. To overcome this challenge, additional ongoing studies (eg, NCT01556009 and NCT01815840) are examining alternative dosing schedules, in particular intermittent dosing, of vismodegib.

Contributors

EHE and JYT contributed to study design, literature search, data collection, data analysis, data interpretation, figures, writing, and editing of the manuscript. DRB, JMM-W, MA, JM, CC, JAL, GU, and MRR contributed to data collection, data interpretation, and editing of the manuscript. GG contributed to data analysis of the manuscript. MSA and AMC contributed to data collection, data analysis, data interpretation, figures, literature search, writing, and editing of the manuscript.

Declaration of interests

JYT and EHE are co-founders, board members, and owners of stock in PellePharm. EHE received grants from Genentech, he is a co-inventor of a Stanford and University of California, San Francisco patent on Patch1 and hedgehog signalling in basal-cell carcinomas that is licensed to Curis Inc. All other authors declare no competing interests.

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