Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma

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Abstract

Background

Mutations in hedgehog pathway genes, primarily genes encoding patched homologue 1 (PTCH1) and smoothened homologue (SMO), occur in basal-cell carcinoma. In a phase 1 clinical trial, we assessed the safety and pharmacokinetics of GDC-0449, a small-molecule inhibitor of SMO, and responses of metastatic or locally advanced basal-cell carcinoma to the drug.

Methods

We selected 33 patients with metastatic or locally advanced basal-cell carcinoma to receive oral GDC-0449 at one of three doses; 17 patients received 150 mg per day, 15 patients received 270 mg per day, and 1 patient received 540 mg per day. We assessed tumor responses with the use of Response Evaluation Criteria in Solid Tumors (RECIST), physical examination, or both. Molecular aspects of the tumors were examined.

Results

The median duration of the study treatment was 9.8 months. Of the 33 patients, 18 had an objective response to GDC-0449, according to assessment on imaging (7 patients), physical examination (10 patients), or both (1 patient). Of the patients who had a response, 2 had a complete response and 16 had a partial response. The other 15 patients had either stable disease (11 patients) or progressive disease (4 patients). Eight grade 3 adverse events that were deemed to be possibly related to the study drug were reported in six patients, including four with fatigue, two with hyponatremia, one with muscle spasm, and one with atrial fibrillation. One grade 4 event, asymptomatic hyponatremia, was judged to be unrelated to GDC-0449. One patient withdrew from the study because of adverse events. We found evidence of hedgehog signaling in tumors that responded to the treatment.

Conclusions

GDC-0449, an orally active small molecule that targets the hedgehog pathway, appears to have antitumor activity in locally advanced or metastatic basal-cell carcinoma. (ClinicalTrials.gov number, NCT00607724.)
Basal-cell carcinoma, the most common skin cancer in the United States, has an estimated annual incidence of 0.1 to 0.5%. The disease is largely caused by exposure to ultraviolet radiation, but there are other risk factors. Surgery cures most cases of basal-cell carcinoma, but in a few patients there is progression to life-threatening, unresectable, locally advanced or metastatic tumors. There is no standard therapy for locally advanced or metastatic basal-cell carcinoma. The survival time in metastatic basal-cell carcinoma varies widely, but the median is 8 months.

Basal-cell carcinoma is associated with mutations in components of the hedgehog signaling pathway. Hedgehog, a key regulator of cell growth and differentiation during development, controls epithelial and mesenchymal interactions in many tissues during embryogenesis. Extracellular hedgehog protein binds to patched homologue 1 (PTCH1), a 12-transmembrane receptor, and prevents PTCH1-mediated inhibition of signaling by smoothened homologue (SMO), a 7-transmembrane protein (Fig. 1A, left). Signaling by SMO results in the activation of transcription factors encoded by GLI family zinc finger (GLI) and consequent induction of hedgehog target genes, including GLI1 and PTCH1. The hedgehog pathway is inactive in adult tissues. However, most basal-cell tumors have mutations in the hedgehog signaling pathway that inactivate PTCH1 (loss-of-function mutation) or, less commonly, constitutively activate SMO (gain-of-function mutation) (Fig. 1A, center). These mutations cause constitutive hedgehog pathway signaling, which in basal-cell carcinomas can mediate unrestrained proliferation of basal cells of the skin. For this reason, blocking the hedgehog pathway may be useful in treating patients with basal-cell carcinoma.

The steroidal alkaloid cyclopamine, a teratogen that induces midline deformities in developing embryos, blocks hedgehog signaling by binding to SMO and inhibiting the activation of downstream hedgehog target genes. The novel SMO inhibitor GDC-0449 was discovered by high-throughput screening of a library of small-molecule compounds and subsequent optimization through medicinal chemistry (Fig. 1A, right). GDC-0449 is a selective hedgehog pathway inhibitor with greater potency and more favorable pharmaceutical properties than cyclopamine. GDC-0449 has antitumor activity in a mouse model of medulloblastoma and in xenograft models of primary human tumor cells, including colorectal cancer and pancreatic carcinoma, in which its effects correlate with blockade of the hedgehog pathway.

A phase 1 trial was initiated to evaluate the safety and adverse-effect profile of daily oral administration of GDC-0449 in patients with metastatic or locally advanced basal-cell carcinoma and other solid tumors. Antitumor activity was observed in the first two patients with basal-cell carcinoma, prompting enrollment of additional patients to evaluate the activity and safety of the drug. This report summarizes the results for all patients with advanced basal-cell carcinoma who were enrolled in the study.

METHODS

STUDY DESIGN

We conducted an open-label, multicenter, two-stage phase 1 trial to evaluate the safety and tolerability of GDC-0449 in patients with a variety of solid tumors that were refractory to standard therapy. In all, 68 patients enrolled in the study at three centers; of these patients, 33 had advanced basal-cell carcinoma.

In stage 1, the dose-escalation stage, we wanted to estimate the maximum tolerated dose of GDC-0449. Patients received a single oral dose of GDC-0449 on day 1, followed by daily administration at the same dose beginning on day 8. Seven patients were assigned to receive 150 mg per day, nine patients 270 mg per day, and four patients 540 mg per day; each dose cohort included one patient with advanced basal-cell carcinoma. GDC-0449 was to be discontinued in patients who had dose-limiting toxic effects or other intolerable side effects or disease progression or in patients who did not benefit from treatment, as decided by the investigator. No dose-limiting toxic effects were observed. The recommended phase 2 dose was 150 mg per day because pharmacokinetic analyses indicated that doses greater than this did not result in higher plasma concentrations of the drug.

In stage 2, we included an expansion cohort that received the recommended phase 2 dose, with the goal of obtaining additional information on pharmacokinetics, pharmacodynamics, and safety; 12 patients (none with advanced basal-cell carcinoma) enrolled in this cohort, and all received...
150 mg per day. The study was amended to include two further cohorts in stage 2. One of these cohorts was added because of evidence of clinical benefit in two patients with advanced basal-cell carcinoma during stage 1; this cohort consisted of 20 patients with advanced basal-cell carcinoma, who were treated with 150 mg per day or 270 mg per day (with the dose chosen on the basis of drug availability) to evaluate the activity and safety of GDC-0449 in this population. The second cohort, which consisted of 16 patients with solid tumors (including 10 with advanced basal-cell carcinoma), was added to investigate the pharmacokinetic properties of a new formulation of GDC-0449 at 150 mg per day. In stage 2, all patients received continuous daily administration of the drug, be-
Panel A shows the hedgehog signal transduction pathway (left), loss-of-PTCH1 mutations (center), and inhibition of smoothened homologue (SMO) signaling by GDC-0449 (right). Hedgehog binding to PTCH1 (left) relieves inhibition of SMO activation by PTCH1. In the absence of PTCH1, because of loss-of-PTCH1 mutations, SMO signaling occurs constitutively (center). GDC-0449 inhibits SMO signaling through direct interaction with SMO (right).

Panel B shows the duration of GDC-0449 therapy and best responses for the 33 patients in the study. Patients were assessed according to either Response Evaluation Criteria in Solid Tumors (RECIST) (mainly for patients with metastatic tumors) or clinical criteria (mainly for patients with locally advanced tumors). Patients 15 and 29 were the only ones with locally advanced disease who could be evaluated radiologically and were assessed according to RECIST. Patients with metastatic disease were evaluated with the use of RECIST, except for Patients 10 and 24, who did not have radiologically measurable disease and were evaluated with the use of clinical measures. Patient 20 was evaluated with the use of both RECIST and clinical measures. Clinical criteria consisted of physical examination for reepithelialization of ulcerated lesions, flattening of nodular lesions, or shrinkage of palpable tumor masses. CR denotes complete response, PD progressive disease, PR partial response, SD and stable disease.

Figure 1 (facing page). Mechanism of Action of GDC-0449 and Response to Treatment.

GDC-0449 was discovered by Genentech and was jointly validated through a series of preclinical studies performed under a collaborative agreement between Genentech and Curis. The study was designed jointly by Genentech and the investigators. Data were collected by the investigators and retained and analyzed by Genentech. The first draft of the manuscript was written by six authors from Genentech and three academic authors. The academic authors had full access to the data, and all authors vouch for the accuracy and completeness of the data and the analysis. The study was reviewed and approved by the institutional review board at each site, according to clinical guidelines. All patients provided written informed consent.

ELIGIBILITY

All patients, who were at least 18 years of age, had histologically confirmed locally advanced or metastatic basal-cell carcinomas that had been documented on pathological analysis and that were considered by the investigator to be refractory to standard therapy. All patients had tumors that could be evaluated on physical examination or radiographic imaging and had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (on a scale ranging from 0 to 5, with higher scores indicating a greater severity of illness). Documentation of a negative pregnancy test was required for women of childbearing potential. GDC-0449 treatment did not begin until more than 3 weeks after the patient’s last therapy or major surgical procedure. Exclusion criteria included major organ dysfunction, a long QT interval or any medication known to prolong the QT interval (because preliminary evaluation of the potential of GDC-0449 to prolong the QT interval was ancillary objective of the study), active infection requiring intravenous antibiotics, pregnancy, other conditions that in the opinion of the investigator would contraindicate investigational drug use, and an inability to swallow pills.

DATA COLLECTION

For the first 6 weeks, all patients underwent weekly physical examination, along with monitoring of vital signs, ECOG performance status, electrocardiographic results, and blood counts and chemical analyses; after that, assessments were performed every 4 weeks.

For patients with radiologically measurable disease (generally, those with metastatic tumors), tumor assessment was performed at baseline, at 8 weeks, and every 8 weeks thereafter with the use of Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.0) to determine stable disease, progressive disease, and best overall response. A complete or partial response was defined as the disappearance of a palpable or visible tumor, and a partial response was defined as a reduction of more than 50% in the diameter of a palpable or visible tumor.

Data concerning adverse events were collected for up to 30 days after the last study treatment. All patients who received any amount of GDC-0449 were included in the safety analyses. Graded adverse events (number and percent) were summarized and reported according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (version 3.0).
Baseline and weekly plasma samples were collected from patients in stages 1 and 2 for the first 4 weeks, with more frequent sampling during the first week for stage 1 and then at approximately monthly intervals. Total plasma levels of GDC-0449 were determined on liquid chromatography–tandem mass spectrometry. The maximum plasma level of GDC-0449 was defined as the highest level that was observed in any patient. The steady-state level of GDC-0449 was calculated from arithmetic averages of two consecutive levels.

Pharmacodynamic assessments of GLI1 expression were carried out on RNA extracted from 4-mm biopsy specimens of noninvolved skin at baseline and at 7 and 21 days after the start of daily drug therapy. Patients were not required to provide tumor-biopsy samples. All samples were processed as described below for stored tumor tissue.

### HEDGEHOG PATHWAY IN STORED TUMOR TISSUE

After the patients provided written informed consent, we evaluated samples of their archival tumor tissue for tumor content and processed the samples for transcriptional profiling or DNA sequence analysis. Expression levels of GLI1 were assessed by TaqMan polymerase-chain-reaction (qPCR) assay and calculated by the $2^{-ΔΔCt}$ method, in which the cycling threshold (Ct) of GLI1 was normalized to the Ct of SMO and expressed as a power of $2^{(ΔCt_{GLI1}−ΔCt_{SMO})}$. (Primer and probe sequences are available in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Control samples of messenger RNA (mRNA) were obtained from formalin-fixed, paraffin-embedded samples of normal skin from subjects who were not enrolled in the study and from commercially available samples of cutaneous basal-cell carcinoma, normal lung, and lung cancer tissue (Asterand and Cytomyx).

DNA for sequence analysis was extracted from stored sections containing at least 30% tumor. Before sequencing, exons 1 to 23 of PTCH1 and exon 9 of SMO were amplified with the use of nested primers on PCR assay (Table 1 in the Supplementary Appendix). Alterations in these genes were confirmed by independent PCR sequencing assays. For Patient 2, homozygosity of the PTCH1 mutation was confirmed by primer extension and mass spectroscopy with the use of matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) for amplified DNA extracted from tumor cells by laser-capture microdissection (MassARRAY, Sequenom).

### RESULTS

#### PATIENTS

From January 2007 through December 2008, we enrolled 33 patients with metastatic or locally advanced basal-cell carcinoma. Three of these patients were enrolled in stage 1 of the study; each of the three received a different daily dose of GDC-0449: 150 mg, 270 mg, or 540 mg. The 30 other patients were enrolled in stage 2; 16 received GDC-0449 at 150 mg per day, and 14 received 270 mg per day. Of the 33 patients, 8 (24%) were women. A total of 18 patients (55%) had metastatic disease, and 15 (45%) had locally advanced disease (Table 1).

### Table 1. Baseline Characteristics of 33 Patients with Basal-Cell Carcinoma.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>Median 53</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td>Male 25 (76)</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td>Female 8 (24)</td>
</tr>
<tr>
<td>Race or ethnic background — no. (%)*</td>
<td>White 32 (97)</td>
</tr>
<tr>
<td>Race or ethnic background — no. (%)*</td>
<td>Latino 1 (3)</td>
</tr>
<tr>
<td>ECOG score — no. (%)†</td>
<td>0 14 (42)</td>
</tr>
<tr>
<td>Type of disease — no. (%)</td>
<td>Metastatic 18 (55)</td>
</tr>
<tr>
<td>Type of disease — no. (%)</td>
<td>Locally advanced 15 (45)</td>
</tr>
<tr>
<td>Previous therapies — no. (%)</td>
<td>Surgery 28 (85)</td>
</tr>
<tr>
<td>Previous therapies — no. (%)</td>
<td>Radiotherapy 19 (58)</td>
</tr>
<tr>
<td>Previous therapies — no. (%)</td>
<td>Systemic therapy 15 (45)</td>
</tr>
</tbody>
</table>

* Race or ethnic background was reported by investigators. † Eastern Cooperative Oncology Group (ECOG) scores range from 0 to 5, with higher scores indicating a greater severity of illness.
Tumor Responses

As of February 28, 2009 (the data cutoff date), all 33 patients had undergone at least one follow-up tumor assessment and could be evaluated for a response to treatment (Fig. 1B). Of the 18 patients with metastatic tumors, 15 had radiologically measurable disease, and 7 of these patients had a partial response, as assessed on imaging only (with 6 responses confirmed and 1 unconfirmed at the time of the data cutoff). Two other patients with metastatic tumors had partial responses, one assessed on both imaging and physical examination and the other on physical examination only. Seven patients with metastatic tumors had stable disease (with six patients assessed with the use of RECIST and one on physical examination), and two had progressive disease as the best response. The overall response rate among the 18 patients with metastatic tumors was 50% (95% confidence interval [CI], 29 to 71).

Of the 15 patients with locally advanced tumors, 13 were assessed on physical examination (clinical response), and 2 with measurable disease were assessed on imaging, according to RECIST. Of these 15 patients, 2 had a complete clinical response, and 7 had a partial clinical response; 4 patients had stable disease as the best response, with a duration of participation in the study ranging from 2.1 to 19.0 months; 2 of the patients had progressive disease. Overall, the response rate in patients with locally advanced tumors was 60% (95% CI, 33 to 83).

As of the data cutoff date, the Kaplan–Meier estimate of the median time of participation in the study was 9.8 months and ongoing, and the median duration of response was 8.8 months and ongoing. Figure 2 shows the clinical benefit of treatment in two patients, with additional photographs and scans in Figure 1 in the Supplementary Appendix.

Adverse Events

No dose-limiting toxic effects or grade 5 events were observed during the study period. A single grade 4 adverse event (asymptomatic hyponatremia) occurred. The following grade 3 adverse events were seen: fatigue (in four patients); hyponatremia, weight loss, and dyspnea (in two patients each); and muscle spasm, atrial fibrillation, aspiration, back pain, corneal abrasion, dehydration, keratitis, lymphopenia, pneumonia, urinary tract infection, and a prolonged QT interval (in one patient each). Eleven grade 2 adverse events that were considered to be related to the study drug occurred (Table 2). A single patient, Patient 11, who had locally advanced tumors and had a partial clinical response, decided to discontinue treatment after 8 months because of ongoing grade 1 adverse events (abdominal pain, fatigue, weight loss, and dysgeusia) and grade 2 anorexia.

Pharmacokinetic and Pharmacodynamic Analyses

Figures 3A and 3B show the concentration–time profiles of GDC-0449 for the 33 patients. The median maximal plasma level was 23.0 μM (interquartile range, 16.8 to 29.7) (Fig. 3B). The median steady-state concentration was 16.1 μM (interquartile range, 13.7 to 21.6). The median time to steady state was 14 days (interquartile range, 7 to 22). Increasing the dose from 150 mg to 270 mg did not result in higher steady-state plasma levels,
with a median steady-state level of 19.8 μM (interquartile range, 13.5 to 25.8) for the 150-mg dose and 15.9 μM (interquartile range, 13.8 to 17.7) for the 270-mg dose. A consistent steady-state total plasma level of GDC-0449 was maintained throughout the treatment period, with no apparent decline at the time of disease progression.

Pharmacodynamic down-modulation in the hedgehog pathway was shown by a decrease in GLI1 expression by more than a factor of two, as compared with pretreatment biopsy-sample analysis, in 10 of 13 patients (data not shown). The extent of GLI1 down-modulation did not correlate with pharmacokinetic levels of GDC-0449 in individual patients.

**Molecular Studies**

GLI1 mRNA expression levels in tumor-biopsy specimens that were obtained from 25 of 26 patients were consistent with expression levels previously observed in cutaneous basal-cell carcinoma (Fig. 3C). GLI1 was overexpressed in tumors obtained from patients with either metastatic or locally advanced tumors, as compared with control samples of normal skin and lung tumor (P<0.001 for all comparisons). GLI1 levels were not elevated in a metastatic liver-biopsy specimen from Patient 33, whose disease progressed during the study. GLI1 mRNA levels were elevated in tissue from two of three additional patients with progressive disease (2\(^{-\Delta\Delta C_t} = 9.7\) and 10.9, normalized against Smo); tissue was not obtained from the third patient.

The entire coding region of the PTCH1 gene and an exon encoding a previously identified activating mutation of SMO (SMO-M2)\(^{15}\) were sequenced from patients’ stored tumor samples that could be evaluated (Table 3 in the Supplementary Appendix). Mutations in the PTCH1 gene, including nonsense and missense mutations, were found in 9 of 10 such specimens. An intronic point mutation disrupting a consensus splice site that was detected in tissue from a lung mass in Patient 2 was found to be homozygous on mass spectrometry of the microdissected tumor epithelium; this finding was consistent with loss of heterozygosity of the PTCH1 tumor suppressor gene (Fig. 2 in the Supplementary Appendix). In addition, the oncogenic SMO-M2 mutation\(^{15}\) was identified in a patient with stable disease, and two PTCH1 mutations were detected in a normal skin-biopsy specimen from a patient with the basal-cell nevus syndrome (Patient 4).

**Table 2. Adverse Events.*  

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
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<td>**Clinical event</td>
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<td></td>
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</tr>
<tr>
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<td>0</td>
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<tr>
<td>Hyponatremia</td>
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<td>1</td>
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<tr>
<td>Muscle spasm</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Dysgeusia</td>
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<tr>
<td>Anorexia</td>
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<tr>
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<tr>
<td>Back pain</td>
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</tr>
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<td>Increase in serum potassium (&gt;5.1 mmol/liter)</td>
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</table>

* All grade 3 and 4 events are listed. Grade 2 events are listed only if investigators considered them to be related to GDC-0449 treatment. A complete list of all grade 2 events is available in Table 2 in the Supplementary Appendix. No grade 5 events were reported. The highest grade of event is reported for each patient.

**Discussion**

In this study, a tumor response to GDC-0449 was seen in some patients with advanced basal-cell carcinoma. Of 33 patients with locally advanced or metastatic tumors, 18 had a response to GDC-0449. Of the remaining 15 patients, 11 had stable disease for up to 10.8 months, and 4 had progressive disease. There were no dose-limiting tox-
ic effects or grade 5 adverse events, and only one grade 4 adverse event occurred during continuous daily administration of GDC-0449 for up to 19 months.

Basal-cell carcinoma is usually treated with surgical excision and rarely recurs or spreads. The patients we treated in this study had advanced tumors that were no longer amenable to conventional treatment options, including surgery, radiotherapy, or systemic therapy.

The molecular mechanisms that drive the development of advanced basal-cell carcinoma have not been previously characterized. We found high levels of GLI1 mRNA expression in tumors from the patients, similar to the levels in more common resectable basal-cell carcinoma and consistent with constitutive activation of the hedgehog pathway. These results, combined with the responses of some tumors to treatment with GDC-0449, suggest that advanced tumors rely on the activation of the hedgehog pathway for growth and maintenance.

Four subjects in our study had progressive disease. Hedgehog signaling was not detected in a liver-tumor sample obtained from one of these patients, who had metastatic basal-cell carcinoma and whose disease rapidly progressed during

Figure 3. Pharmacokinetic Analysis and Molecular Correlates of GDC-0449 Administration.
Panel A shows the pharmacokinetic analysis of GDC-0449 for each of the 33 enrolled patients, according to dose. Three patients were exposed to a single dose on day 0, followed by repeated daily administration of GDC-0449, starting on day 7. The remaining 30 patients received daily doses, starting on day 0. Panel B shows mean concentration–time data for 30 patients who received either 150 mg or 270 mg of GDC-0449. The vertical lines represent standard deviations. Panel C shows elevated GLI1 messenger RNA (mRNA) expression in archival tissue obtained from 25 of 26 patients with metastatic or locally advanced basal-cell carcinoma (BCC), as compared with control specimens. GLI1 expression levels were assessed with the use of real-time polymerase-chain-reaction assay and calculated by the 2^−ΔCt method, in which the cycling threshold (Ct) of GLI1 was normalized to the Ct of SMO and expressed as a power of 2 (2^ΔCt(GLI1)−ΔCt(SMO)). The mean (2Mean(−ΔCt)) and standard deviation (2SD(−ΔCt)) are indicated below the chart for each tissue type. Data for control subjects with either normal or malignant lung samples are included, since some specimens of metastatic basal-cell carcinoma represented lung metastases.
the study. Two of the four patients with progressive disease had increased hedgehog pathway signaling, which suggests that unknown mechanisms underlie the lack of benefit of GDC-0449 or that the stored tissue was not representative of the unresponsive tumor. Our findings confirm the participation of the hedgehog pathway in basal-cell carcinoma and suggest that inhibition of the hedgehog pathway can be useful in treating inoperable tumors.

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