Secondary (acquired) resistance of a tumor to a chemotherapeutic agent is characterized by regrowth of a tumor after initial shrinkage. This is distinct from primary resistance, in which a tumor never responds to treatment, a separate topic from our current study. The Smoothened (SMO) inhibitor, vismodegib (GDC-0449), has recently been shown to be useful in phase 1 and 2 clinical trials for locally advanced basal cell carcinomas (laBCCs) (defined as inoperable owing to multiple postsurgical recurrences or incurable with surgery without significant deformity or loss of function) or metastatic BCCs (mBCCs). Collectively, laBCCs and mBCCs are termed advanced BCCs, and vismodegib treatment was approved in 2012 by the US Food and Drug Administration for this indication. Our case series describes a previously unreported phenomenon of BCC tumor regrowth within or immediately adjacent to (within 1 cm) the prior tumor bed of a vismodegib-responsive tumor while the patient is still undergoing continuous vismodegib treatment. We call this phenomenon secondary (acquired) resistance.

Methods. We conducted a retrospective medical chart review, approved by the Stanford human subjects panel, examining the records of 28 consequent patients with laBCC or mBCC treated with continuous administration of vismodegib and observed from 4 to 162 weeks (until any-cause death or last clinic visit). All patients were seen at Stanford Hospital and Clinics on a monthly basis. All patients had been enrolled as part of 3 vismodegib clinical trials with identical inclusion and exclusion criteria (NCT00833417, NCT00959647, and NCT01160250), including at least 1 laBCC or mBCC, and had no treatment breaks during follow-up time. Twenty-one patients were men, and 7 were women.

Results. Of treated patients, 21% developed at least 1 tumor regrowth while undergoing continuous vismodegib treatment, with a mean (SD) time to detected regrowth by clinical examination of 56.4 (52.3) weeks (Table). The BCCs with regrowth represented 5% of all BCCs (including laBCCs, mBCCs, and nonadvanced BCCs) observed during vismodegib treatment (12 of 152) (Table). Clinically, all patients with tumor regrowth also had at least 1 concurrent laBCC during treatment.

Three of 5 patients with tumor regrowth had Gorlin syndrome, an inherited tumor susceptibility syndrome previously reported to give rise to BCCs with exquisite sensitivity to SMO inhibition. In 2 patients, the regrown BCC had a BCC subtype not present in the pretreatment biopsy specimens. For instance, the Figure shows an example of a patient whose pretreatment histologic findings revealed a nodular BCC (Figure, A). After complete clinical response (Figure, B), the patient experienced regrowth in 2 areas of the original lesion, and the superior area of regrowth contained both superficial and nodular BCC (Figure, C). The 12 BCCs from the 6 patients with regrowth showed a variety of subtypes (Table): nodular (n=2), micronodular (n=2), superficial (n=2), infiltrative (n=5), and basosquamous (n=1). None of the 8 patients with mBCC developed regrowth after shrinkage of their BCCs or developed a new BCC on their skin while undergoing continuous vismodegib treatment.

Comment. The reasons for tumor regrowth are currently unclear and are the subject of much research. Our cases suggest that a single BCC lesion can be heterogeneous on a cellular or molecular level. Tumor regrowth could be attributed to a number of factors. Clinically, all of our patients with regrowth had at least 1 other concurrent laBCC. In addition, it is possible that some tumor cells could develop mutations in the SMO protein resulting in decreased binding of the drug. Regrowth may

### Table. Characteristics of Study Patients

<table>
<thead>
<tr>
<th>BCC Category</th>
<th>Patients, No.</th>
<th>Patients With a Regrown BCC</th>
<th>Time to Regrowth, Mean (SD) wk</th>
<th>All BCCs With Regrowth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>28</td>
<td>6/28 (21)</td>
<td>56.4 (52.3)</td>
<td>12/230 (5)</td>
</tr>
<tr>
<td>laBCC</td>
<td>20</td>
<td>6/20 (30)</td>
<td>56.4 (52.3)</td>
<td>12/152 (8)</td>
</tr>
<tr>
<td>mBCC</td>
<td>8</td>
<td>0/8 (0)</td>
<td>NA</td>
<td>0/78 (0)</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>5</td>
<td>3/5 (60)</td>
<td>55.3 (85.4)</td>
<td>6/133 (5)</td>
</tr>
<tr>
<td>Non-Gorlin syndrome</td>
<td>23</td>
<td>3/23 (13)</td>
<td>62.3 (42.1)</td>
<td>6/97 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinomas; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable.

a Six of these 28 patients developed tumor regrowth during vismodegib therapy (21%); unless otherwise noted, data are reported as number of patients in the category/total number of patients (percentage).
also occur in the setting of clonal evolution for tumor cells that have a compensatory amplification of genes downstream from SMO such as Gli.\textsuperscript{1,3}

In individuals with multiple resistant BCCs, the isogenic background of a single individual may facilitate molecular studies of these resistant BCCs because some of the tumors may become resistant through multiple mechanisms. Future efforts to attack or prevent resistance in BCCs may involve the use of more than 1 drug at a time to target multiple pathways that contribute to abnormal basal cell growth.\textsuperscript{4,5}

We were surprised that our case series did not show secondary resistance in the 8 patients with mBCC. It is possible that with longer follow-up times, mBCCs may be observed to acquire resistance while the patient is undergoing vismodegib treatment. In addition, larger sample sizes may be needed to observe this phenomenon: the regrowth rate we observed was only 1 in 5 in patients with mBCC.

Because of the risk of regrowth, frequent skin examinations of patients undergoing treatment with vismodegib are essential to monitor for acquired resistance, even if the original tumor appears to be gone on clinical examination. When identified and biopsied early, these secondarily resistant BCCs are more likely to be treated effectively. Non-SMO inhibitor treatments such as surgical excision can be essential to optimize patient outcomes.

With increased vismodegib usage, it is likely that tumor regrowth may be an increasing phenomenon. Future studies with larger numbers of patients observed for longer periods are needed to confirm our observations, identify factors associated with regrowth, and characterize the molecular mechanisms by which regrowth occurs.

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Accepted for Publication: May 25, 2012.
Published Online: August 20, 2012. doi:10.1001/archdermatol.2012.2354

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Financial Disclosure: Drs Chang and Oro are clinical investigators in studies sponsored by Genentech, Infinity, and Novartis.

Funding/Support: Research for this article was funded by National Institutes of Health grant R01AR046786 (Dr Oro).

Role of the Sponsors: The sponsor had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review or approval of the manuscript.


Computerized Interactive Educational Tools Used to Improve Use of Sun-Protective Clothing and Sunscreen: A Randomized Controlled Study

Skinsafe\textsuperscript{2} is a computer-assisted learning (CAL) program developed to educate patients on melanoma risk factors, melanoma symptoms, and the importance of sun-protective behavior. The program asks users to complete in a single sitting (<30 minutes) computerized modules containing a combination of interactive and didactic seg-