A Phase II, Randomized, Placebo-Controlled Study of Vismodegib as Maintenance Therapy in Patients with Ovarian Cancer in Second or Third Complete Remission

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Abstract

Purpose: Hedgehog pathway inhibition has been suggested as a potential maintenance treatment approach in ovarian cancer through disruption of tumor-stromal interactions. Vismodegib is an orally available Hedgehog pathway inhibitor with clinical activity in advanced basal cell carcinoma and medulloblastoma. This phase II, randomized, double-blind, placebo-controlled trial was designed to provide a preliminary estimate of efficacy in patients with ovarian cancer in second or third complete remission (CR).

Experimental Design: Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in second or third CR were randomized 1:1 to vismodegib (GDC-0449; 150 mg daily) or placebo three to 14 weeks after completing chemotherapy. Treatment continued until radiographic progression or toxicity. The primary endpoint was investigator-assessed progression-free survival (PFS).

Results: One hundred four patients were randomized to vismodegib (n = 52) or placebo (n = 52); median PFS was 7.5 months and 5.8 months, respectively [HR 0.79; 95% confidence interval (CI), 0.46–1.35]. The HR was 0.66 (95% CI, 0.36–1.20) for second CR patients (n = 84) and 1.79 (95% CI, 0.50–6.48) for third CR patients (n = 20). The most common adverse events in the vismodegib arm were dysgeusia/ageusia, muscle spasms, and alopecia. Grade 3/4 adverse events occurred in 12 patients (23.1%) with vismodegib and six (11.5%) with placebo. Hedgehog expression was detected in 13.5% of archival tissues.

Conclusions: In this study, the sought magnitude of increase in PFS was not achieved for vismodegib maintenance versus placebo in patients with ovarian cancer in second or third CR. The frequency of Hedgehog ligand expression was lower than expected.

Introduction

In the United States, an estimated 21,880 new cases of ovarian cancer were diagnosed in 2010, with an estimated 13,850 deaths (1). Most patients with ovarian cancer are diagnosed with advanced disease and are treated with surgery followed by either intravenous or intraperitoneal chemotherapy (2) usually consisting of a platinum agent combined with a taxane (3–6). Primary peritoneal and fallopian tube carcinoma are now considered in the same category and are treated in the same way as ovarian cancer (2).

Although many patients respond to initial therapy, the majority will experience disease recurrence and require additional chemotherapy. Therefore, maintenance treatment has been studied both in the first-line and relapsed disease settings with the aim of decreasing or delaying recurrence. In an earlier randomized study of maintenance paclitaxel, PFS was increased after 12 months of treatment compared with after 3 months (7). However, concerns over toxicity and the lack of an overall survival benefit have reduced uptake of this approach. More recently, positive results have been reported from randomized trials of maintenance therapy in the first- and second-line settings for bevacizumab and PARP inhibitors (8–11). Further studies are planned, but it is already becoming clear that as new approaches are adopted, therapeutic resistance will develop. For this reason, there continues to be a pressing need to identify novel treatments that will prolong PFS in patients with ovarian cancer, particularly targeted agents that have minimal cumulative toxicity and can be conveniently administered.

The Hedgehog signaling pathway regulates epithelial and mesenchymal interactions in a variety of tissues during
mammalian embryogenesis and represents a new target for cancer therapy. Extracellular Hedgehog ligand binds to Patched (PTCH1), a 12-pass transmembrane receptor. Hedgehog binding relieves the inhibitory effect of PTCH1 on Smoothened (SMO), a 7-pass transmembrane domain receptor (12). Signal transduction by SMO then leads to activation and nuclear localization of GLI1 transcription factors and the induction of Hedgehog target genes, many of which are involved in proliferation, survival, and angiogenesis.

In the vast majority of basal cell carcinomas (BCC) and a subset of medulloblastomas, genetic alterations in Hedgehog pathway components, such as PTCH1 and SMO, lead to ligand-independent activation of SMO and constitutive activity of the Hedgehog pathway (13). In contrast, excessive or inappropriate expression of the Hedgehog ligand has been implicated in the pathogenesis of other sporadic cancers including pancreatic and other gastrointestinal, prostate, lung, and ovarian cancers (14–19). Recent studies have shown a paracrine mechanism of Hedgehog pathway activation in some tumor types, wherein Hedgehog ligand secreted by tumor cells acts on neighboring stromal cells, subsequently contributing to tumorigenesis (Fig. 1A; ref. 20). Furthermore, both Hedgehog ligand protein expression and mRNA expression are increased in a subset of ovarian cancer specimens (19, 21). The naturally occurring Hedgehog pathway inhibitor cyclopamine has been shown to decrease proliferation rates and induce apoptosis in ovarian carcinoma cell lines (22). A recent study has shown inhibition of serous ovarian cancer xenograft growth by the Hedgehog pathway inhibitor IPI-926, when given in combination with chemotherapy and then as maintenance therapy (19).

The Hedgehog pathway inhibitor vismodegib (Erivedge; formerly known as GDC-0449; Genentech) has shown oral bioavailability and potent antitumor activity in a variety of primary human tumor xenografts (21). Vismodegib was evaluated in a phase I, dose-escalation study of patients with refractory solid tumors, with activity seen in patients with advanced BCC and 1 patient with disseminated medulloblastoma (23–25). It was generally well tolerated; the most common toxicities were mild-to-moderate fatigue, anorexia, muscle spasms, alopecia, and dysgeusia, and the recommended dose for phase II clinical studies was 150 mg orally, once daily. Results of a pivotal study of vismodegib in advanced BCC (26) led to the approval of vismodegib by the U.S. Food and Drug Administration in 2012. Vismodegib and other Hedgehog pathway inhibitors are currently under study for other cancer types (27).

On the basis of these results and the hypothesis that vismodegib could inhibit tumor growth of low-volume disease (where tumor–stroma interaction may be particularly important) mediated through paracrine Hedgehog signaling, a phase II, randomized, double-blind, placebo-controlled trial was initiated in patients with ovarian cancer. The objective was to provide a preliminary estimate of the clinical benefit of maintenance therapy with vismodegib in the setting of second or third complete remission (CR), as measured by investigator-determined PFS using radiographic assessment.

Materials and Methods

Study population and eligibility

All patients were female, 18 years or older, and had histologically confirmed epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma in second or third CR. Patients had received chemotherapy (platinum based and/or nonplatinum based) for recurrent disease, and had achieved a CR after their most recent chemotherapy regimen. CR was defined as no symptoms or evidence of disease, and had achieved a CR after their most recent chemotherapy regimen. CR was defined as no symptoms of persistent cancer, computed tomography (CT) scan of the chest/abdomen/pelvis without evidence of ovarian cancer within 4 weeks of randomization, and normal cancer antigen-125 (CA-125; measured within 2 weeks of randomization) following completion of the most recent chemotherapy regimen. Patients received their last dose of chemotherapy 3 to 14 weeks before randomization. All patients had baseline Eastern Cooperative Oncology Group performance status (ECOG PS) 1 or less and had adequate laboratory-defined organ function. Archival tumor tissue was requested from all patients.

Study design

Patients were randomized 1:1 to receive vismodegib or placebo (Fig. 1B). Randomization was stratified by second versus third CR status. Patients received daily oral vismodegib 150 mg or placebo until evidence of radiographic progression or intolerable toxicities most probably
attributable to vismodegib. The continuous dosing schedule of vismodegib was chosen based on the pharmacokinetic properties characterized in the phase I study (23, 28). Study treatment was to be taken at the same time each day with or without food, and compliance checks were conducted at each clinic visit.

Treatment with vismodegib or placebo could be interrupted for up to 4 weeks pending recovery from toxicity or for up to 8 weeks for a planned surgical procedure. Patients who discontinued study treatment were followed for survival approximately every 3 months until death, loss to follow-up, or study termination. Concurrent antitumor therapy was not permitted.

Data on adverse events were collected for all patients from the day of randomization to 45 days after the last dose of study treatment or the initiation of new antitumor therapy, whichever was earlier.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board or ethics committee at each site. All patients provided written informed consent.

**Efficacy assessments**

PFS was defined as the time from randomization to the first occurrence of investigator-assessed radiographic progression or death from any cause. CT assessments were conducted every 8 weeks; radiographic progression was defined as the appearance of a new lesion consistent with recurrent disease, including new-onset or worsening ascites. Increasing levels of CA-125 in the absence of radiographic progression were not to be interpreted as progression or as a criterion for discontinuation of study treatment. Patients who discontinued study treatment before documented radiographic progression were to continue scheduled tumor assessments to document the date of progression.

**Biomarker assessments**

Quantitative reverse transcriptase PCR (qRT-PCR) profiling was conducted in archival tumor tissue for Hedgehog
ligands—the target of vismodegib (SMO) and the transcriptional target gene GLI1.

Archival tumor specimens were verified by a pathologist before macrodissection to enrich for tumor if overall tumor content was approximately less than 70%. Tissue scraped from serially cut slides was deparaffinized using Envirene reagent (Hardy Diagnostics) before isolation of RNA using the Roche High Pure formalin-fixed paraffin-embedded (FFPE) RNA Micro Kit (Roche Diagnostics). RNA was reversed transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) with random primers. PCR was carried out using the TaqMan Universal PCR Master Mix (Applied Biosystems), with the following cycling conditions: 50°C for 2 minutes; 95°C for 10 minutes; and 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. qRT-PCR profiling of Hedgehog ligands, the target of vismodegib (SMO), and the transcriptional target gene GLI1 was conducted. To detect both the Sonic Hedgehog (SHH) and Indian Hedgehog (IHH) ligand transcripts within the same reaction, an assay (SHH + IHH) was designed to cross-react with both ligand transcripts. In addition, assays were designed to specifically detect either the SHH or IHH ligand transcripts. All assays were tested for amplification efficiency on RNA isolated from FFPE specimens and for lack of genomic DNA amplification. For analyses, Hedgehog pathway gene expression was normalized to the average cycling threshold (Ct) of 3 housekeeping genes (GUSB, SDHA, and UBC). Primers/probes used in this study are shown in Supplementary Table S1.

**Statistical analysis**

The primary efficacy endpoint in this study was the HR for PFS using the stratified Cox model. Patients who did not meet the criteria for disease progression but who died within 45 days of last treatment dose were treated as having progressed for analysis of PFS. The stratification factor for the stratified Cox model was remission history (second or third CR). This primary analysis included a 90% confidence interval (CI) for the stratified HR for PFS. Stratified and unstratified log-rank tests were also conducted. PFS curves and medians within each treatment arm and by remission status were estimated by Kaplan–Meier methodology. In an exploratory analysis, PFS was also assessed as the time from randomization until evidence of CA-125 progression, radiographic progression (as determined by the investigator), or death from any cause.

Patients who did not meet the criteria for disease progression and who did not die were censored at the time of last tumor assessment. Patients lost to follow-up were analyzed as censored observations on the last date that they were progression free plus 1 day. If no post-randomization tumor assessment was available, the observation was censored on the day after the randomization date. Overall survival was defined from the time of patient randomization. For survival analyses, patients lost to follow-up were analyzed as censored observations on the date of last contact.

The sample size of approximately 100 patients was based on the precision for estimating the HR for PFS with 51 PFS events. In a recent study of patients in second CR after treatment with platinum-based therapy, it was

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Figure 2. CONSORT study diagram.
estimated that the median PFS for this patient population was 10.8 months (29); accounting for approximately 4 months of chemotherapy, we assumed PFS for this maintenance study to be approximately 6 months. Therefore, for an estimated HR of 0.73 (or an increase in median PFS from 6.0–8.2 months assuming exponential PFS), the approximate 90% CI for the HR would be 0.46 to 1.15. This trial was hypothesis generating and was only able to detect a relatively large benefit of vismodegib. Therefore, formal hypothesis testing was limited in that, statistically negative outcomes would not necessarily rule out clinically significant treatment effects.

Results

Patient population

Between December 2008 and December 2009, 104 patients from 40 international sites were randomized to receive vismodegib (n = 52) or placebo (n = 52; Fig. 2). All patients received at least 1 dose of study drug and were evaluable for safety. The analyses used a data cutoff date of May 15, 2010, corresponding to the protocol-specified final analysis to be conducted when approximately 51 PFS events had been reported.

Baseline patient demographic and disease characteristics were generally well balanced between treatment groups, with the exception of histology: a slightly higher proportion of patients in the vismodegib arm had serous histology (78.8% vs. 61.5% in the placebo arm) and clear cell histology (7.7% vs. 1.9%, respectively; Table 1). Most patients were in second CR (placebo 84.6%, vismodegib 76.9%) with the remainder in third CR.

**Efficacy**

PFS from time of randomization for patients in the vismodegib arm was 7.5 months compared with 5.8 months for placebo, with an HR of 0.79 (95% CI, 0.46–1.35; P = 0.39; Fig. 3A). When PFS was assessed by remission status, among the 84 patients in second CR, those receiving vismodegib experienced a median PFS of 7.5 months compared with 5.6 months for placebo, with an HR of 0.44 (95% CI, 0.36–1.20; P = 0.17; Fig. 3B). For the small subset of 20 patients in third CR (vismodegib n = 12, placebo n = 8), median PFS was 5.6 months for vismodegib compared with 7.5 months for placebo (HR 1.79; 95% CI, 0.50–6.48; P = 0.37).

PFS was also analyzed using a combination of radiographic and CA-125 criteria (similar to the Gynecologic Cancer InterGroup criteria; ref. 30). Patients whose tumors did not secrete CA-125 were not evaluable for this analysis. A total of 99 patients had CA-125–secreting

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**Table 1. Demographic and baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 52)</th>
<th>Vismodegib (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years Mean</td>
<td>58.6</td>
<td>57.3</td>
</tr>
<tr>
<td>Median</td>
<td>58.0</td>
<td>58.0</td>
</tr>
<tr>
<td>(Range)</td>
<td>38–80</td>
<td>33–84</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>50 (96.2)</td>
<td>48 (92.3)</td>
</tr>
<tr>
<td>African-American</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.9)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Othera</td>
<td>0</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41 (78.8)</td>
<td>37 (71.2)</td>
</tr>
<tr>
<td>1</td>
<td>11 (21.2)</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>Remission status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second CR</td>
<td>44 (84.6)</td>
<td>40 (76.9)</td>
</tr>
<tr>
<td>Third CR</td>
<td>8 (15.4)</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>Disease type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>49 (94.2)</td>
<td>51 (98.1)</td>
</tr>
<tr>
<td>Primary peritoneal carcinoma</td>
<td>2 (3.8)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Fallopian tube carcinoma</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>32 (61.5)</td>
<td>41 (78.8)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>9 (17.3)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Transitional cell</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1 (1.9)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (15.4)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Time since last therapy, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.7 (3.2)</td>
<td>7.0 (2.8)</td>
</tr>
<tr>
<td>Median</td>
<td>6.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Range</td>
<td>3–14</td>
<td>3–14</td>
</tr>
</tbody>
</table>

*Not available, Native American, or multiple.*

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Clin Cancer Res; 18(23) December 1, 2012 6513
tumors, 55 of whom had progressive disease events. The median PFS was the same in both treatment arms (5.8 months). The HR for PFS, stratified by remission status, was 0.73 (95% CI, 0.42–1.26).

As of the data cutoff (May 15, 2010), 3 deaths had occurred (1 in the placebo arm and 2 in the vismodegib arm), therefore analysis of overall survival was not conducted.

**Biomarker analyses**

A secondary objective was to evaluate the relationship between Hedgehog ligand expression in archival tissue and efficacy. Approximately 85% of patients had tissue evaluable for Hedgehog ligands by qRT-PCR. The prevalence of detectable Hedgehog ligand expression (13.5%) was lower than expected; results previously obtained using banked tumor tissue had suggested that a subset of ovarian cancers express elevated levels of Hedgehog ligand (21). Because of the low prevalence of detectable Hedgehog ligand expression, a correlation between Hedgehog ligand expression and clinical benefit could not be determined (Fig. 4). Exploratory analyses of the relationship between PFS and expression levels of SMO (the target of vismodegib) or GLI1 (a downstream biomarker of Hedgehog pathway activation) also did not suggest any correlation (Fig. 4).

**Safety**

The most common adverse events (all grades) in vismodegib-treated patients were dysgeusia/ageusia (71.2%), muscle spasms (63.5%), and alopecia (48.1%; Table 2).
The most frequently observed adverse event in the placebo arm was fatigue (26.9% in both placebo and vismodegib arms). The overall safety profile of vismodegib was consistent with that reported in previous single-agent studies (25).

Within the vismodegib arm, 23.1% of patients experienced a grade 3 or more adverse event at any time versus 11.5% of patients in the placebo arm. The most frequently reported grade 3 or more adverse events were elevated liver enzymes (3 patients), muscle spasms (3 patients), and abdominal pain (2 patients), all in the vismodegib arm. The only grade 4 adverse events observed were abdominal pain and muscle spasms (both in the vismodegib arm). No grade 5 adverse events were reported.

**Study drug exposure and discontinuations**

The duration of study drug exposure in each arm was longer for patients randomized to placebo (median, 5.6 months; range, 0–15 months) than for those randomized to vismodegib (median, 4.9 months; range, 1–13 months). At the data cutoff date, 40 of 52 patients in the vismodegib arm and 35 of 52 in the placebo arm had discontinued study drug. Disease progression was the reason for discontinuation in 24 patients in the vismodegib arm compared with 31 in the placebo arm (Fig. 2). Conversely, adverse event (n = 6) or patient decision (n = 9) was the reason for discontinuation in the vismodegib arm compared with patient decision (n = 3) in the placebo group. The adverse events precipitating discontinuation of the 6 vismodegib-treated patients were: mucositis, muscle spasms, dysgeusia, increased hepatic enzymes, dry mouth, alopecia, diarrhea, and anorexia.

**Discussion**

The ideal agent for maintenance treatment of patients with ovarian cancer should have substantial efficacy and...
Table 2. Adverse events in more than 10% of patients in either arm (all grades), and grade 3/4 adverse events in 2 or more patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 52)</th>
<th>Vismodegib (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events in more than 10% of patients in either arm (all grades)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia/ageusia</td>
<td>10 (19.2)</td>
<td>37 (71.2)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>33 (63.5)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4 (7.7)</td>
<td>25 (48.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (15.4)</td>
<td>17 (32.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (26.9)</td>
<td>16 (30.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (9.6)</td>
<td>11 (21.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (9.6)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (1.9)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>3 (5.8)</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (15.4)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5.8)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>2 (3.8)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (11.5)</td>
<td>5 (9.6)</td>
</tr>
</tbody>
</table>

Grade 3/4 adverse events in 2 or more patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 52)</th>
<th>Vismodegib (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver enzyme elevation</td>
<td>0</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>ALT, AST, GGT, or increased hepatic enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2 (3.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

have Hedgehog ligand overexpression compared with prior studies (19, 21) conducted on banked tumor specimens. For example, it is possible that Hedgehog ligand overexpression is associated with chemotherapy resistance that could prevent patients from achieving CR (and therefore being eligible for this study). Alternatively, it is also possible that Hedgehog ligand overexpression is actually associated with a lower probability of relapse, leading to a lower prevalence of Hedgehog-positive ovarian cancer in this study population. In a recent study describing molecular subtypes of ovarian cancer (31), Indian Hedgehog expression specifically associated with a molecular subtype (C6) characterized by good prognosis, provides indirect support for this hypothesis.

These study results suggest that the paracrine (ligand-driven) model of Hedgehog pathway activity may be less meaningful in ovarian cancer, despite the preclinical scientific rationale. Similarly, there was no incremental benefit observed for vismodegib treatment in a recent placebo-controlled trial of patients with metastatic colorectal cancer who received vismodegib or placebo in combination with bevacizumab and chemotherapy (32). Nevertheless, the numerically improved PFS observed for vismodegib-treated patients in this study suggests that further studies incorporating Hedgehog pathway inhibitors in patients with ovarian cancer could be considered, if an appropriate strategy for patient selection can be identified.

Disclosure of Potential Conflicts of Interest

I. Fu is employed by Genentech, a member of the Roche Group, as a Scientific Manager and has ownership interest (including patents) in Roche.

R. L. Yauch is employed by Genentech as a scientist and has ownership interest (including patents) and stock ownership in Roche. I. Chang is employed by Genentech and owns Roche stock. J. C. Reddy is employed by Genentech as an Associate Group Medical Director and owns Roche stock. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: S. B. Kaye, I. Chang, J. C. Reddy


Acquisition of data (provided animals, acquired and managed patients, provided facilities): S. B. Kaye, L. Fehrenbacher, R. Holloway, A. Amit, B. Karlan, B. Slomovitz, P. Sabbatini, I. Fu, J. C. Reddy

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. B. Kaye, L. Fehrenbacher, B. Karlan, R. L. Yauch, I. Chang, J. C. Reddy

Writing, review, and/or revision of the manuscript: S. B. Kaye, L. Fehrenbacher, R. Holloway, A. Amit, B. Karlan, B. Slomovitz, P. Sabbatini, I. Fu, R. L. Yauch, I. Chang, J. C. Reddy

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Karlan, I. Fu

Study supervision: S. B. Kaye, A. Amit, B. Karlan, J. C. Reddy

Sample processing and RT-PCR assay: L. Fu

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Hedgehog Inhibition with Vismodegib in Ovarian Cancer

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References


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