A Phase I Trial of Liposomal Doxorubicin, Bevacizumab, and Temsirolimus in Patients with Advanced Gynecologic and Breast Malignancies

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Abstract

Purpose: Liposomal doxorubicin (D) and bevacizumab (A) are active single agents in gynecologic and breast malignancies which share a resistance mechanism: upregulation of hypoxia inducible factor (HIF-1α). We, therefore, added temsirolimus (T), which inhibits HIF-1α, to D and A (DAT). Trial objectives were assessment of safety, preliminary efficacy, and identification of biological response correlates.

Patients and Methods: Cycle length was 21 days, with IV D, A, and T on day 1; T on days 8 and 15 (3+3 dose-escalation design with expansion cohorts). Mutational assays for PIK3CA, BRAF, KRAS, and immunohistochemistry for PTEN loss were conducted.

Results: This article details 74 patients with gynecologic and breast malignancies who received at least one dose of drug on study. Median patient age: 52 (27–79); prior regimens: 4 (1–11). Responses: 1 (1.4%) complete response (CR), 14 (18.9%) partial responses (PR), and 13 (17.6%) with stable disease (SD) ≥ 6 months (total = 37.9%). The most common grade 1 toxicities were fatigue (27%) and anemia (20.2%). Notable grade 3/4 toxicities: thrombocytopenia (9.5%), mucositis (6.7%), and bowel perforation (2.7%). PIK3CA mutations or PTEN loss were identified in 25 of 59 (42.3%) of tested patients. Among these, nine (36%) achieved CR/PR and four (16%) had SD ≥ 6 months (CR+PR+SD ≥ 6 months = 52%).

Conclusions: DAT is well tolerated with manageable side effects. Responses observed warrant further evaluation. Mutational analyses were notable for a high percentage of responders with phosphoinositide-3-kinase pathway aberrations. Clin Cancer Res; 17(21); 6840–6. ©2011 AACR.

Introduction

Anthracycline antibiotics have a broad spectrum of antineoplastic action. Liposomal doxorubicin (D) is a pegylated, liposomal encapsulated form of doxorubicin which has shown activity in a number of solid tumors. In contrast to doxorubicin, D exhibits less nonspecific drug delivery to normal tissues and is associated with lower peak plasma levels. These features account for its more tolerable side effect profile in comparison with free doxorubicin (1, 2).

A number of resistance mechanisms mediate anthracycline resistance to chemotherapy (3, 4). Recently, upregulation of the transcription factor hypoxia-inducible factor alpha (HIF-1α), with subsequent increases in the production of proteins that promote angiogenesis, anaerobic metabolism, and other cellular survival pathways has been shown as an important mechanism of anthracycline resistance (5–7).

Angiogenesis, the formation of new blood vessels from existing vasculature, is essential for tumor growth and metastasis (8). Members of the VEGF family of cytokines are among the most potent proangiogenic molecules. Bevacizumab (A), the most widely used VEGF inhibitor, is a chimeric murine/human IgG antibody that targets the VEGF ligand (9). As with anthracyclines, multiple mechanisms have been described which confer resistance to bevacizumab. Central among them is hypoxia-induced HIF-1α upregulation (10).

The phosphatidylinositol-3-kinase (PI3K) signaling pathway is crucial to many aspects of normal cell growth and survival. Accordingly, its dysregulation plays a pivotal role in carcinogenesis, the development of metastatic competence, and therapy resistance. Consequently, there is great interest in the development of targeted inhibitors of key PI3K pathway molecules. Of particular interest to us, during the development of this trial, was the high prevalence of...
PI3K signaling abnormalities, including PIK3CA mutations and PTEN loss, described in both gynecologic and breast cancers (11, 12). Temsirolimus (T) is a derivative of the drug sirolimus, an inhibitor of the mTOR complex (13). mTOR is a critical downstream mediator of PI3K signaling, which when activated, modulates cell proliferation via a number of downstream targets (11). In this manner, mTOR inhibitors have been shown to have significant anticancer properties. Importantly, mTOR inhibitors, particularly (T), also have potent HIF-1α inhibitory properties (14).

Rationale for the combination of DAT

Each of the 3 drugs was chosen on the basis its proven antitumor activity in both gynecologic and breast malignancies. In addition, because HIF-1α upregulation is a key mediator of chemoresistance to both D and A, we postulated that (T) could provide at least additive antitumor activity when administered in combination with D and A (DAT). Because these 3 agents have mostly nonoverlapping toxicities, we anticipated that it would be possible to administer them together at near-maximal single-agent doses.

Patients and Methods

Study design and dosing

This was a single institution, phase I, open-label, sequential dose-escalation study, with a standard 3 + 3 design open to all patient with solid tumors. It was Institutional Review Board (IRB) approved and all patients provided informed consent. This article addresses the subset of patients with gynecologic and breast cancers that were treated on the study (N = 74 of the 117 total treated).

Primary endpoints were to establish the maximum tolerated dose (MTD) and characterize dose-limiting toxicities (DLT). Secondary endpoints included a preliminary assessment of antitumor efficacy, safety profiling, and the establishment of biological corollaries for prediction of tumor response and tolerability. Six dose levels were originally planned. As the MTD was not met at dose level 6, the protocol was amended with the addition of an additional dose level (Table 1).

Drug administration was repeated on a 21-day cycle with all 3 drugs given on day 1 and T administered weekly on days 8 and 15 (Table 1). If 1 patient in a cohort experienced a DLT during the first cycle, 3 additional patients were enrolled and treated at that dose level. If at any time, more than 33% of patients in a cohort experienced a DLT then that cohort was closed to additional patients. Of note, early in the trial, multiple significant responses were observed and the protocol was amended to allow for cohort expansion for up to 15 patients from malignancies in which response criteria were met. This resulted in expansion cohorts in uterine, ovarian, breast, cervical, colorectal, parotid, adrenocortical, and malignant thymoma. No gynecologic or breast cancer patients were treated at dose level 7.

Table 1. Dose-escalation schedule (21-day cycle)*

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Bevacizumab (IV; day 1) mg/kg</th>
<th>Liposomal doxorubicin (IV; day 1) mg/m²</th>
<th>Temsirolimus (IV; days 1, 8, and 15) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>10</td>
<td>12.5</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>20</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
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<td>20</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>7*</td>
<td>15</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

*The original protocol included dose levels 1 to 6, however, at dose level 6, there were no DLTs, so the protocol was amended to include dose level 7. After multiple responses were seen in lower dose levels, the protocol was amended to include expansion cohorts for up to 15 patients from malignancies in which response criteria were met. This resulted in expansion cohorts in uterine, ovarian, breast, cervical, colorectal, parotid, adrenocortical, and malignant thymoma. No gynecologic or breast cancer patients were treated at dose level 7.
sions if specific response criteria were met. This resulted in cohort expansions in the following malignancies: uterus, ovary, breast, cervix, malignant thymoma, parotid, adrenocortico, and colorectal.

Administration of (DAT) continued until unacceptable toxicity or disease progression occurred, or total cumulative anthracycline dose exceeded 550 mg/m². Dose delays and reductions were left to the discretion of the treating physician. DLTs were defined as follows: Any grade 3 or 4 nonhematologic toxicity as defined in the National Cancer Institute CTC v3.0 that was possibly, probably, or definitely related to any of the 3 study medications, with the following exceptions: (a) any grade 4 hematologic toxicity lasting less than 2 weeks, and (b) any grade 4 nausea, or vomiting lasting less than 5 days (15). DLTs had to occur within the first cycle of treatment.

Eligibility criteria

Key inclusion criteria were age 12 or older; measurable, histologically documented solid tumors refractory to standard treatment or for which no standard therapy was available; Eastern Cooperative Oncology Group (ECOG) performance status 2 or less (exceptions required IRB approval); absolute neutrophil count ≥1.5 × 10⁹/L; platelet count ≥100.0 × 10⁹/L; serum creatinine ≤3.0 mg/dL, alanine transaminase 5 times or less the upper limit of normal (ULN), with the exception of patients with significant liver metastases, who were allowed to have values 8 times or less the ULN; bilirubin ≤2.0 mg/dL, and cardiac left ventricular ejection fraction 50% or more without evidence of congestive heart failure. Key exclusion criteria were poorly controlled hypertension (systolic blood pressure >150 mm Hg, diastolic pressure >100 mm Hg), patients with clinically significant cardiovascular disease, prior cumulative doxorubicin dose >300 mg/m², and pregnancy. Prior exposure to anthracyclines and VEGF inhibitors were not exclusion criteria for study entry, nor were patients with a history of venous thromboembolism excluded.

Assessment of tumor response

Tumor measurements were done by a staff radiologist pretreatment and every 2 cycles thereafter, as well as by a departmental Response Evaluation Criteria in Solid Tumors (RECIST) measurement team. Measurable target lesions were evaluated for response using RECIST (16, 17). For purposes of this article, prolonged stable disease (SD) was defined as trial enrollment without dose delays of more than 2 weeks in total for 180 or more days. Adverse events were recorded from day 1 through 30 days after the last dose and were graded on the basis of Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0).

Molecular assays for biological markers: PIK3CA, KRAS, BRAF mutations, and PTEN loss

We included Clinical Laboratory Improvement Amendment (CLIA) certified mutational or immunohistochemical assays, as appropriate, for PIK3CA, KRAS, and BRAF mutations as well as PTEN loss. The tests were done within the Division of Pathology and Laboratory Medicine at MD Anderson. Archival formalin-fixed, paraffin-embedded tissue blocks or tissue from fine-needle aspiration or surgical biopsies were used to test for BRAF mutations. DNA was extracted from microdissected paraffin embedded tumor sections and analyzed using a PCR-based DNA sequencing method for BRAF codons 468–474, codons 595–600, and mutations of exon 15 by pyrosequencing, as previously described (18). Tests for PIK3CA and K-RAS mutations were done using a similar method. Exons 9 (codons 532–554) and 20 (codons 1,011–1,062) for examined PIK3CA mutations, and codons 12, 13, and 61 were examined for KRAS mutations (7). PTEN loss was assessed using immunohistochemistry (12) (monoclonal mouse anti-human PTEN, clone 6H2.1, Dako; ref. 12).

At trial initiation, IRB approved pre- and posttreatment image-guided percutaneous tumor biopsies were offered to patients with the specified intention to identify molecular corollaries for response assessment. Mutational analyses for PIK3CA, BRAF, KRAS, and PTEN loss as described above, and reverse-phase proteomic analysis (RPPA) assays for more than 100 cell signaling proteins grouped by signaling system were planned. We found recruitment of patients for these biopsies to be difficult; to date there are 3 patients who have completed the pre- and posttreatment biopsies; as a result, these batched tissue samples have not yet been processed for reporting purposes.

Statistical analysis

Descriptive statistics are provided for all endpoints using STATA v10.0. Continuous measurements are summarized using mean, standard deviation, median, range, number of patients, and percentages. Time to treatment failure (TTF) and overall survival (OS) were calculated using the method of Kaplan and Meier in days, from date of enrollment to disenrollment or death from any cause, whichever came first. Patients still on trial at the time of last assessment were censored. A waterfall plot depicting best RECIST responses by percent is presented in Fig. 1.

Figure 1. Individual patients (disease sites by color) are represented with vertical bars on the X-axis. Best RECIST response (%) is depicted on the Y-axis. Patients with progressive disease as their best response are depicted as +20%.
Results

Patient characteristics and disposition

Seventy-seven women with advanced, metastatic, chemotherapy-refractory ovarian, uterine, cervix, and breast malignancies were enrolled. Two of these had deteriorating functional status prior to dosing and were subsequently disenrolled. One patient voluntarily disenrolled prior to first dosing citing financial reasons. Seventy-four patients were treated and evaluated. Demographic and clinical characteristics are summarized in Table 2. The median age of patients was 52 years (range = 27–75 years). The median number of prior therapies for metastatic disease was 4. Fifty-two deaths occurred; 50 were attributed to disease progression and 2 were thought, possibly, due to adverse effects of 1 or more of the study drugs. The median number of cycles completed for all patients was 5 (range = 0–27). For patients with SD or better, the median number of cycles completed was seven (range = 2–27).

Overall survival and time to treatment failure

Seventy of 74 patients had survival information available. The remaining 4 were lost to follow-up. Median OS was 214 days (95% CI = 185–312). At time of censoring, 67 of 74 (90.5%) were disenrolled. The overall median TTF was 112 days (95% CI: 89–147).

Dose escalation, DLT, tolerability, and MTD

Patients were enrolled in accordance with the planned 3 + 3 study design until dose level 4, at which point our IRB approved expansion cohorts as described in the Methods section; they were filled using dose levels shown in Table 1 (in diseases in which activity was observed, expansions were permitted at the highest dose level found to be safe as of that date). This resulted in dose escalations in cancers of the ovary, endometrium, and cervix. Dose escalation for the remaining 3 levels continued in accordance with the original escalation plan. There were 2 DLTs observed during the study; however, both involved nongynecologic cancer patients (grade 4 thrombocytopenia) within dose level 7 (liposomal doxorubicin 40 mg/m², bevacizumab 15 mg/kg, and temsirolimus 25 mg). These were the first 2 patients treated at dose level 7, and no further gynecologic or breast cancer patients were enrolled at that dose level. The MTD for the study was therefore level 6 (Table 1).

Safety

All 74 (100%) patients experienced at least 1 adverse event that was at least possibly drug related. These events were mostly grade 1 or grade 2 and reversible. Grade 2 fatigue (27%), anemia (20.2%), neutropenia (18.5%), and mucositis (17.5%) were the most common events, requiring dose modification and trial discontinuation in 7 (9.5%) and 4 (5.4%) patients, respectively. Grade 3 or 4 toxicities were as follows: thrombocytopenia (9.5%), mucositis (6.7%), cardiac (4.1%), gastrointestinal [bowel perforation (2.7%)] and genitourinary [vesicovaginal fistula (1.4%)]. Of note, 3 of 7 (43%) patients who experienced grade 3 to 4 thrombocytopenia were enrolled, with baseline platelet levels less than 125 × 10⁹/L. There were 2 (2.7%) possible treatment related events of fatal colonic perforation (dose levels 1 and 3). One of the patients had ovarian cancer; the other patient had endometrial cancer. Both patients had bulky pelvic tumor and both had completed pelvic radiotherapy; both events were associated with precipitous declines in serum Ca125 level of each patient.

Response data and efficacy

All patients are assessable for response. Five patients (6.7%) discontinued treatment for social reasons, without formal resting or evidence of clinical progression before completing 2 cycles. These patients were classified as having progressive disease (PD). Of the remaining patients, 1 (1.4%) had a complete response (CR) and 14 (18.9%) had a partial response (PR; CR + PR = 20.3%). 13 patients (17.6%) had prolonged SD. Responses by disease site are detailed in Table 3.

Among 18 patients with epithelial uterine cancer (excluding 3 patients with stromal cancers), 5 (27.8%) had a PR and 4 patients (22.2%) had prolonged SD.
(PR + prolonged SD = 50%). Among 16 patients with epithelial ovarian cancer (excluding 4 patients with non-high grade epithelial histologies), 3 (18.7%) had a PR and 4 patients (25%) had prolonged SD (PR + prolonged SD = 43.7%). Among 20 patients with breast cancer, 1 (5%) had a CR and 4 (25%) had a PR (CR + PR = 30%); 4 patients (20%) had prolonged SD (CR + PR + prolonged SD = 45%). Of interest is that 3 of the breast cancer responders (1 CR, 2 PRs) had metaplastic breast cancer, a notoriously chemoresistant triple-negative histologic subtype. Two of 13 (15.4%) patients with cervical cancer achieved a PR and 1 (7.7%) had prolonged SD (PR + prolonged SD = 23.1%). Of note, 5 of the 15 (33%) patients with a CR or PR had previously progressed on anthracycline chemotherapy (median cumulative dose 200 mg/m²; range = 160–360). Responses by individual patient are characterized in Table 4.

Seven patients remained on study at time of censoring. The one patient (metaplastic breast cancer) who achieved a CR is still on study at 530 days. This patient was without evidence of disease after 6 cycles; after 8 cycles, D and A were discontinued and she has remained on maintenance T. Among all patients, median TTF was 112 days (95% CI: 89–147). Among patients with a PR, average TTF was

### Table 3. Response data by disease site and histology

<table>
<thead>
<tr>
<th>Disease site histology</th>
<th>Patients treated</th>
<th>CR N (%)</th>
<th>PR N (%)</th>
<th>SD ≥ 6 months N (%)</th>
<th>CR + PR + SD ≥ 6 months N (%)</th>
<th>Median # cycles completed (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus Epithelial</td>
<td>21</td>
<td>5 (27.8)</td>
<td>4 (22.2)</td>
<td>9 (50)</td>
<td>5 (1–20)</td>
<td></td>
</tr>
<tr>
<td>Ovary Epithelial (high grade)</td>
<td>16</td>
<td>3 (18.8)</td>
<td>4 (25)</td>
<td>7 (43.8)</td>
<td>6 (1–13)</td>
<td></td>
</tr>
<tr>
<td>Ovary Epithelial (low grade)</td>
<td>1</td>
<td>2</td>
<td>4 (1–8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary Granulosa</td>
<td>2</td>
<td></td>
<td>4 (1–8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary Sarcoma</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary Cervix</td>
<td>13*</td>
<td>2 (15.4)</td>
<td>1 (7.7)</td>
<td>3 (23.1)</td>
<td>3 (1–6)</td>
<td></td>
</tr>
<tr>
<td>Breast Ductal</td>
<td>11</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>4 (1–8)</td>
<td></td>
</tr>
<tr>
<td>Breast Lobular</td>
<td>1</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>9 (7–12)</td>
<td></td>
</tr>
<tr>
<td>Breast Metaplastic</td>
<td>8</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>5 (4–8)</td>
<td></td>
</tr>
</tbody>
</table>

*Organ specific histologic subtypes grouped to determine denominator.

### Table 4. CR and PR characterization by patient

<table>
<thead>
<tr>
<th>Response</th>
<th>Disease site</th>
<th>Histology</th>
<th>Dose level</th>
<th># Prior cytotoxic regimens</th>
<th>Prior anthracycline history</th>
<th># Cycles completed</th>
</tr>
</thead>
</table>
172 days (range = 46–468; 95% CI: 100–246). Patients with SD after 2 cycles had an average TTF equal to 133 days (range = 42–272; 95% CI: 112–154), and TTF for patients with PD was 42 days (range = 6–89; 95% CI: 29–55).

Table 5. details responses, OS, and TTF by dose level.

Responses were seen among a variety of histologic subtypes. Notable characteristics of each responder are detailed in Table 3. Estrogen receptor (ER) status was known among 3 of the 4 uterine cancer responders; all 3 of these were positive. ER status was known for all breast cancer patients. Three of the 5 breast cancer responders had ER-positive tumors.

Molecular testing for PIK3CA, KRAS, bRAF mutations, PTEN loss, and association with response

When archival cell blocks for patients were available, CLIA certified testing was done for bRAF and PIK3CA mutations as well as PTEN loss. PIK3CA mutational status was known for 57 of 74 (77%) patients and was positive in 16 (28%). PTEN status was known for 25 of 74 (33.8%) patients, and PTEN loss was identified in 11 (44%). BRAF status was known for 45 of 74 (60.8%) patients, and 2 (4.4%) were positive. KRAS status was known for 49 of 74 (66.2%) patients, and 8 (16.3%) were positive. Four (25%) of the 16 patients with a PIK3CA mutation, 5 (45.5%) of 11 patients with PTEN loss, 2 (25%) of the 8 patients with a KRAS mutation and 1 (50%) of the 2 patients with a BRAF mutation achieved a response. Among the 15 responders (CR + PR), PIK3CA and PTEN status were known in 9 (60%) and 5 (33.3%), respectively. Four (44.4%) of the 9 responders for whom PIK3CA mutational status was known were positive, and 3 (60%) of the 5 responders for whom PTEN status was known were found to have PTEN loss. PIK3CA mutations or PTEN loss were identified in 25 of 59 (42.3%) tested patients. Among these, 9 (36%) achieved CR/PR and 4 (16%) had SD ≥ 6 months (CR + PR + SD ≥ 6 months = 52%).

Discussion

Treatment planning for patients with chemorefractory gynecologic and breast cancers is challenging because there is little definitive data with regard to optimal therapy in patients who have failed first-line agents (19–21). In addition, the majority of such patients are heavily pretreated and unable to tolerate full-dose cytotoxic regimens. As insights into tumor resistance biology have improved, we are increasingly able to exploit these mechanisms to more effectively treat patients with chemorefractory disease (4, 10, 22–26). The biological rationale for this combination was that each drug has proven efficacy as a single agent in multiple solid tumors, each is relatively tolerable with nonoverlapping toxicities, and 2 of the 3 drugs (D and A) share HIF-1α as a resistance mechanism. In addition, PI3K pathway aberrations are common in breast and gynecologic cancers (27, 28). This fact makes an mTOR inhibitor, such as T, a potentially ideal drug for use in combination with D and A (29).

The overall response rate (ORR = CR + PR) in this population of heavily pretreated patients (median number of prior cytotoxic regimens = 4) was 15 of 74 (20.3%). Responses by disease site among epithelial uterine, ovarian, breast, and cervical carcinomas were 27.8%, 18.8%, 25%, and 15.4%, respectively. When patients with prolonged SD are considered with responders, total response plus prolonged SD was 50%, 43.8%, 45%, and 23.1%, respectively.

Whether the responses observed are due simply to the additive effects of the 3 drugs, or synergism resulting from T-mediated HIF-1α inhibition is unknown. Unfortunately, our plan for pre- and posttreatment tissue analyses did not result in an adequate number of tissue samples to be of use for answering this question. Future investigations should emphasize the obtaining of pre- and posttreatment samples so that biological corollaries for a clinical response can be identified. Of particular interest in this study were the percentages of patients with PI3K pathway aberrations that achieved a response or prolonged SD; of 25 patients with either PIK3CA mutations or PTEN loss, 9 (36%) achieved a PR, and the rate of response plus SD for at least 6 months was 52%.

This combination is relatively safe and well tolerated, with predictable and largely manageable adverse effects. As expected, the primary issue with tolerability was thrombocytopenia, and this was managed without the need for disenrollment in all but one patient. The incidence of mucositis was consistent with that seen with D alone and was also manageable without disenrollment for all but one patient. Also, notable were 2 colonic perforations. These are well described in association with A in ovarian cancer patients. The incidence of bowel perforation in our population was within the range of that described by previous investigations (30–32). The
most serious toxicity was bowel perforation, seen in 2 patients with bulky disease and prior radiation treatment, both of whom showed a precipitous early fall in CA125. This significant problem might be due to bevacizumab and/or temsirolimus and/or rapid response and/or the disease itself.

Further study of DAT in larger populations of patients with gynecologic and breast malignancies is warranted. The recommended dose for phase II/III study is liposomal doxorubicin dosed at 20 to 30 mg/m² every 21 days, bevacizumab 15 mg/kg every 21 days, and temsirolimus 25 mg weekly using a 21-day cycle. Studies that include enrichment for patients with PIK3CA mutations or PTEN loss may be especially worthwhile.

Disclosure of Potential Conflicts of Interest

R. Kurzrock is the Senior Editor of Molecular Cancer Therapeutics. No potential conflicts of interest were disclosed.

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