Phase I, Dose-Escalation Study of the Targeted Cytotoxic LHRH Analog AEZS-108 in Patients with Castration- and Taxane-Resistant Prostate Cancer

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Abstract

Purpose: AEZS-108, formerly AN-152, is a cytotoxic hybrid molecule consisting of a luteinizing hormone-releasing hormone (LHRH) agonist moiety covalently coupled to doxorubicin, allowing it to deliver doxorubicin selectively to cells expressing LHRH receptors. LHRH receptors are expressed on the cell membrane of many tumors, including prostate cancer. This phase I study determined the maximum tolerated dose (MTD) of AEZS-108 in men with taxane- and castration-resistant prostate cancer (CRPC) while providing additional information on the safety profile and efficacy of this agent.

Experimental Design: AEZS-108 was administered as an intravenous infusion every 21 days until progression or unacceptable toxicity in cohorts of 3 or 6 patients until the MTD was reached. Blood was collected for capture of circulating tumor cells (CTC) to visualize internalization of AEZS-108, an autofluorescent molecule.

Results: The MTD of AEZS-108 in this cohort was 210 mg/m², which was lower than that seen in a phase I study conducted in women with endometrial or ovarian cancers. The dose-limiting toxicity was persistent neutropenia. Three patients had a PSA response with an additional 10 patients maintaining PSA stable disease. Of the 10 patients evaluable by RECIST criteria, 9 achieved stable disease. AEZS-108 internalization in CTCs was routinely visualized using its autofluorescence.

Conclusion: These findings show that AEZS-108 has an acceptable safety profile and a signal of efficacy, lowering PSA in heavily pretreated patients with prostate cancer, and that internalization of AEZS-108 in prostate cancer CTCs may be a viable pharmacodynamic marker. A phase II study in men with prostate cancer is ongoing. Clin Cancer Res; 20(24); 6277–83. ©2014 AACR.

Introduction

In the United States, prostate cancer is the second leading cause of death in men (1). The current standard treatment for metastatic prostate cancer is androgen deprivation therapy (ADT); while initially effective, the benefit from ADT is transitory, with progression occurring after a median of 18 months (2). Recently developed, next-generation hormonal agents, such as abiraterone 1000 mg daily (3) and enzalutamide 160 mg daily (4), provide additional treatment options for castration-resistant prostate cancer (CRPC), but eventually, patients will consider treatment with cytotoxic chemotherapy. Several other agents are approved in this setting, including mitoxantrone, docetaxel, cabazitaxel, and sipuleucel-T (5). The use of these agents is regrettably empiric and limited by toxicity, with no useful predictive markers to guide their use. Effective cytotoxic agents with accompanying predictive biomarkers remain an unmet need in CRPC.

Receptors for luteinizing hormone-releasing hormone (LHRH) are expressed on the gonadotroph cells of the pituitary gland. This forms the basis for the use of LHRH agonists, typically leuprolide or goserelin, in advanced prostate cancer; their use leads to downregulation of LHRH receptors and a decrease in signaling through the pituitary–hypothalamic–gonadal axis, ultimately resulting in a decrease in the secretion of gonadal testosterone (6). While expression of LHRH receptors may not be common in...
Translational Relevance

This manuscript describes a phase I trial of AEZS-108 (formerly AN-152), a hybrid molecule coupling an LHRH agonist with doxorubicin. The structure of this compound permits targeted delivery of the cytotoxic doxorubicin moiety to cells bearing LHRH receptors. LHRH receptors are expressed on various tumors, including castration-resistant prostate cancer. Here, we report the results from the phase I trial of AEZS-108 in men with refractory prostate cancer, providing a maximum tolerated dose and reporting early signs of efficacy in heavily pretreated patients. In addition, we demonstrate the ability to visualize internalization of this drug in captured circulating tumor cells, exploiting the autofluorescence of doxorubicin. This has the potential to be a valuable pharmacodynamic predictive marker and is being explored in an ongoing phase II trial of AEZS-108 in men with prostate cancer.

normal, nonpituitary tissue, these receptors are highly expressed on malignant tissue, including cancers of the lung, ovary, endometrium, bladder, kidney, breast, colon, and prostate (7–15). We have previously reported that expression of LHRH receptor on prostate cancer cells persists despite prolonged exposure to LHRH agonists (16). AEZS-108 (formerly, AN-152) is a rationally designed, cytotoxic LHRH conjugate (17). This compound consists of an LHRH analog covalently linked to the anthracycline doxorubicin, a broadly active cytotoxic agent (18). The structure of AEZS-108 preserves the cytotoxicity of doxorubicin while providing a high binding affinity to LHRH receptors. AEZS-108 accumulates on the surface of cells expressing LHRH receptors, triggering internalization of the drug, where doxorubicin can provoke the desired antitumor response. The hypothesis is that this agent, which targets the cytotoxic agent to cells bearing LHRH receptors, will reduce peripheral toxicity while increasing efficacy. AEZS-108 has shown consistent activity in both in vitro and in vivo prostate cancer models (18, 19). The first-in-human study of AEZS-108 was completed in women with ovarian, endometrial, or breast cancer and established a maximum tolerated dose (MTD) of 267 mg/m² where the dose-limiting toxicity (DLT) was leukopenia and neutropenia (20). In this limited study of 17 patients, 3 achieved a partial or complete response and 4 achieved stable disease. Given the persistent expression of LHRH receptors in prostate cancer cells (16) and the lack of expression on most normal tissues, AEZS-108 represents a promising targeted therapeutic agent for CRPC. Because the experience with AEZS-108 was limited to female patients, we designed a dose-escalation study of AEZS-108 in men with CRPC before launching a phase II trial (NC101240629).

The primary objective of this phase I study was to determine the MTD of AEZS-108 given intravenously every 21 days in men with CRPC. Secondary outcomes included the assessment of safety and tolerability and preliminary antitumor activity of AEZS-108 in this patient population. In an effort to develop a predictive, pharmacodynamic biomarker, we captured circulating tumor cells (CTC) from treated patients before and after treatment with AEZS-108 to detect internalization of this agent, exploiting the autofluorescent nature of doxorubicin (21).

Materials and Methods

Patient eligibility

This single institution, open-label, dose-escalation trial was approved by the Health Sciences Institutional Review Board of the University of Southern California (Los Angeles, CA) in accordance with the Helsinki Declaration. All patients provided written, informed consent. Participation was limited to men with prostate cancer who had documented progression with at least one prior hormone treatment, which must have included LHRH agonist therapy, and at least one prior chemotherapy regimen, which must have included taxane therapy. Men were eligible if they had an Eastern Cooperative Oncology Group performance status of 0–2, had recovered from the acute and late effects of prior therapy, and had adequate hematologic and organ function. Patients with brain metastases, prior anthracycline or anthracenedione therapy, or an impaired left ventricular ejection fraction (LVEF < 50%) were excluded. Because of the possibility of receptor competition with AEZS-108, patients were required to discontinue any LHRH agonist therapy and eligibility began 2 weeks after their first missed scheduled dose to permit an adequate wash-out.

Dosage and administration

AEZS-108 (Aeterna Zentaris) was administered intravenously through a central venous catheter over 2 hours every 21 days for up to 6 cycles; treatment beyond 6 cycles was left at the discretion of the principal investigator. Premedication included dexamethasone 8 mg given intravenously 30 minutes before chemotherapy and a 5-HT3 antagonist anti-emetic. Concomitant use of bone-targeted agents was permitted and LHRH agonist therapy was withheld through the duration of the trial, but resumed upon discontinuation of AEZS-108.

Study design

AEZS-108 was given intravenously in 21-day cycles. Only three cohorts were planned in this accelerated model: 160 mg/m², which was well tolerated in the published phase I trial in women, 267 mg/m², the established MTD in women, and 210 mg/m², an intermediate dose. DLT was defined using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as any of the following adverse effects attributed to the study drug during the first cycle: grade 3 or 4 neutropenia lasting longer than 7 days, grade 4 thrombocytopenia, grade 3 thrombocytopenia lasting longer than 7 days or with hemorrhage, development of clinical congestive heart failure or reduction in LVEF to <50%, evidence of pituitary dysfunction based on scheduled thyroid function tests or cosyntropin stimulation tests, any
delay in treatment beyond 21 days, or any grade 3 or higher nonhematologic toxicity (except for nausea or vomiting in the absence of optimal antiemetic therapy; grade 3 diarrhea not treated with optimal medical therapy or that improved to grade 2 or lower within 2 weeks; and grade 3 elevation in aspartate aminotransferase or alanine aminotransferase that resolved to grade 2 or lower within 7 days). Hematopoietic growth factors were not permitted as primary prophylaxis during the first cycle.

AEZS-108 was dose escalated using standard "3+3" rules until the MTD was reached. At least 3 evaluable patients were treated in each cohort. If no patients at a given dose level experienced a DLT, the dose was escalated. If two patients at a dose level experienced a DLT, that dose was considered to be above the MTD and escalation was stopped in favor of deescalation. If exactly one of the first 3 patients treated at a dose level experienced a DLT, 3 additional patients were treated at that dose level. If a second patient at that dose level experienced a DLT, the MTD was considered exceeded, but if no additional patients experienced a DLT, the MTD was reached. The MTD was thus defined as the maximum dose in which no more than 1 of 6 evaluable patients experienced a DLT. All patients treated would be evaluated for safety and efficacy. Patients would only be evaluable for dose escalation if they completed one full cycle of therapy or experienced a DLT. Patients not evaluable for dose escalation were permitted but dose escalation and dose re-escalation in a given patient were not permitted.

Assessment of safety and response

Patients were assessed for safety at each clinic visit. A physical examination with laboratory studies was performed every 21 days before administration of AEZS-108. AEZS-108 has not been associated with cardiomyopathy in animal studies or in early human trials (22), but because it does contain doxorubicin, which can be cardiotoxic, scheduled LVEF assessment with a cardiac multigated acquisition (MUGA) scan was performed after every third cycle of therapy or experienced a DLT. Patients not evaluable for dose escalation were replaced. Patients were permitted to continue AEZS-108 until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, completion of 6 cycles, or patient or physician preference. Dose reductions were permitted but dose escalation and dose re-escalation in a given patient were not permitted.

CTC analysis

CTCs were captured using a polycarbonate microfilter containing size-based micropores measuring 7 to 8 microns in diameter evenly distributed over the membrane surface. Use of this membrane has been previously described (24). Briefly, a 7.5 mL sample of blood collected in EDTA was diluted with 6 mL of PBS and fixed with 10% formalin. Blood was collected at baseline and 1 to 3 hours after administration of AEZS-108 in cycles 1, 3, and 6 and immediately processed in this manner. The fixed cells were then passed through the filter using a syringe. After air drying, the cells on the filter were stained with mouse anti-PSA antibody (1:200; Dako) and Texas red-conjugated anti-mouse IgG (1:100; Vector Laboratories). The stained cells were mounted with 4',6-diamidino-2-phenylindole (DAPI)-containing mounting media (Life Technologies) and analyzed using fluorescence microscopy. Cells were stained with DAPI and for PSA. Fluorescent microscopy was used to determine whether the captured prostate cancer CTCs displayed any evidence of autofluorescence.

Results

Patient characteristics

Between November 2010 and December 2011, 18 patients were accrued to this study (Table 1), all of whom met the inclusion criteria and were treated in dose-escalated cohorts. The median age was 70 (range, 48–88) and 41% of patients had a Gleason score of 8 or higher. Median PSA at time of study entry was 106 ng/dL (range 8–1,624). Patients received a median of two prior chemotherapy regimens (range, 1–5). Of the 18 total patients, 3 received abiraterone, 2 received enzalutamide, and 7 received cabazitaxel before enrollment. Progression before study entry was assessed by radiographic criteria in 39% and by symptomatic rise in PSA in 61%. All patients were evaluable for PSA

<table>
<thead>
<tr>
<th>Table 1. Patient demographics and clinical characteristics</th>
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<tr>
<td><strong>Total eligible patients</strong></td>
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<tr>
<td><strong>Dose level for AEZS-108</strong></td>
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<tr>
<td>160 mg/m²</td>
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<td>210 mg/m²</td>
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<tr>
<td>267 mg/m²</td>
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<tr>
<td><strong>Age in years</strong></td>
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<td><strong>Gleason score</strong></td>
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<tr>
<td><strong>Prior treatment</strong></td>
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<td>Surgery</td>
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<tr>
<td>Radiation</td>
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<td>Chemotherapy</td>
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<tr>
<td><strong>Number of regimens</strong></td>
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<td>(median, range)</td>
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response and 10 (56%) were evaluable by RECIST version 1.1 criteria. Sites of disease for each patient are detailed in Supplementary Table S1.

Dose escalation
All 18 patients were treated with AEZS-108 in dose-escalating cohorts of 160 mg/m² (n = 3), 210 mg/m² (n = 8), and 267 mg/m² (n = 7). All patients were evaluable for toxicity (Table 2) but 2 patients at 210 mg/m² and 1 patient at 267 mg/m² were inevaluable for dose escalation due to lack of follow-up and were replaced. DLTs occurred in 3 patients: two patients at 267 mg/m² and one patient at 210 mg/m². In each case, the DLT was grade 4 neutropenia lasting more than 7 days, though recovery was seen in each of these patients and each was successfully retreated at a lower dose. The 210 mg/m² dose was thus defined as the MTD in this study.

Safety findings
AEZS-108 was reasonably well tolerated in this older patient population (Supplementary Table S2). Grade 3 and 4 adverse events were seen in 13 patients (Table 2, 72%). Of these adverse events, anemia, lymphopenia, leukopenia, neutropenia, and febrile neutropenia were observed in two or more patients on each dose level. The majority of treatment-related adverse events were observed at dose level 267 mg/m². Cardiac function did not significantly decrease during treatment and never fell below 50% (Supplementary Table S3). No patients developed hypothyroidism during therapy and cosyntropin stimulation tests did not reveal any pituitary abnormalities (Supplementary Table S3).

Treatment administered and efficacy
Patients received a median of 4 cycles (range 1–8) with 33% of patients receiving at least 6 cycles and 2 patients completing 8 cycles. Using PSA Working Group Criteria, 3 patients experienced a PR (a PSA decline of >50% from baseline confirmed with a second value at least 4 weeks later), 10 patients had SD, and 5 had PD as their best PSA response (Table 3; Fig. 1). Of the 10 patients evaluable by RECIST version 1.1 criteria, 9 achieved SD and 1 had PD as their best response (Fig. 2). Median PFS was 3.9 [95% confidence interval (CI): 2.5–11.7] months (17 events, 1 censored at the time of initiating new therapy, Fig. 3) and median OS was 8.9 (95% CI: 5.8–30.6) months (11 events, Fig. 3). Median follow-up was of 17.2 months (range: 14.4–30.6 months). Serial testosterone values were available for 14 patients (the other 4 had only a baseline value). Of these 14, 3 experienced a decrease, 7 remained the same, and 4 had a rise in their testosterone, one of which exceeded 50 ng/dL.

CTC analysis
Prostate cancer CTCs were consistently captured from patients using the slot filter method. No autofluorescence was noted on baseline samples (Fig. 4). CTCs captured 1 to 3 hours after administration of AEZS-108 consistently showed autofluorescence, demonstrating internalization of AEZS-108 and the doxorubicin moiety.
Discussion

Initial therapy for advanced prostate cancer remains ADT and the recent development of novel hormonal agents, such as abiraterone and enzalutamide, offers additional options for men with CRPC (3–5). While these agents are often highly effective, resistance invariably develops and the majority of patients will ultimately be considered for treatment with traditional chemotherapy. The development of a targeted strategy in this setting is appealing, in part due to the advanced age and comorbidities of most men with advanced prostate cancer.

LHRH receptors are expressed on the cell membranes of prostate cancer cells, even after prolonged exposure to LHRH agonists (16) and while the function of these receptors remains unclear, their presence alone represents a potential context of vulnerability. AEZS-108 combines the binding affinity of an LHRH analog with a cytotoxic doxorubicin molecule, allowing targeted delivery of this antitumor agent to prostate cancer cells (18).

This study describes the first experience with AEZS-108 in male patients. Interestingly, the MTD in this study was lower than that seen in females (20). Overall, the safety profile was favorable, with reversible toxicities. A significant proportion of these heavily pretreated patients received six or more cycles. The DLTs seen were all related to persistent neutropenia and the use of colony-stimulating factors such as pegylated G-CSF in the ongoing phase II study may abrogate these effects. There were several theoretical safety risks with AEZS-108 explored in this trial. First, due to the presence of the doxorubicin molecule, there was a potential risk of cardiotoxicity, as doxorubicin is associated with a dilated cardiomyopathy. AEZS-108 doses of 210 mg/m² and 267 mg/m² contain 60.2 mg/m² and 76.6 mg/m² of doxorubicin, respectively. The targeted nature of AEZS-108 might prevent this toxicity and preclinical studies in dogs did not show evidence of cardiomyopathy after repeated dosing. Still, patients enrolled on this study were monitored closely, with serial MUGA scans to measure cardiac function. No patients experienced a significant drop in ejection fraction, all patients retained an ejection fraction over 50%, and no patients developed clinical symptoms of congestive heart failure even in subjects whose cumulative doxorubicin dose exceeded 300 mg/m². While our experience is reassuring, cardiac function will be closely monitored as experience with this agent increases.

Another theoretical risk was a potential damage to the pituitary. Pituitary gonadotrophs express LHRH receptors (6) and preclinical studies did demonstrate selective damage to these cells manifested by decreased hormone secretion in animals treated with AEZS-108 (22). In the case of advanced prostate cancer, however, the possible decrease in luteinizing hormone and follicle-stimulating hormone secretion would result in decreased testosterone synthesis, an additive and desirable consequence in men with prostate cancer. The pituitary has other functions, including secretion of thyrotropin (thyroid stimulating hormone, TSH) and corticotropin (adrenocorticotropic hormone, ACTH) but the cells responsible for these functions do not express LHRH receptors and should not be damaged by AEZS-108.

To be certain that there was no unexpected pituitary toxicity, thyroid function was monitored by regular thyroid function blood tests. No significant changes in TSH or thyroid

<table>
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<th>Table 3. Summary of responses</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Total treatment cycles received</td>
</tr>
<tr>
<td>&lt;6 cycles</td>
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<tr>
<td>≥6 cycles</td>
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<tr>
<td>Median (range)</td>
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<tr>
<td>Best PSA response</td>
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<td>PR</td>
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<tr>
<td>SD</td>
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<tr>
<td>PD</td>
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<tr>
<td>OS (months)</td>
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<td>Progression-free survival (months)</td>
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Figure 1. Waterfall plot of maximal PSA response (n = 18).

Figure 2. Waterfall plot of best RECIST version 1.1 response (n = 10).

Figure 3. Waterfall plot of best response change from baseline (%).
hormone levels were detected through the course of this study. Similarly, the ACTH axis was monitored with scheduled cosyntropin stimulation assays (25) and again, no abnormalities were detected in this study.

There was also a potential concern regarding cessation of therapy with LHRH agonists. It is currently standard to continue LHRH agonist therapy, indefinitely, though the benefits of this practice are not entirely clear. In a retrospective study of 205 patients enrolled in five clinical trials conducted by SWOG, 33 patients who did not undergo surgical castration received therapy for CRPC. Of these 33, 26 did not continue exogenous hormonal therapy and there was no difference in survival between these men and those treated with orchietomy (26). We felt that it was necessary to discontinue LHRH agonist use in our study, to avoid potential competition with AEZS-108 for tumoral LHRH receptors, and that this did not pose undue risk to study subjects. In fact, we hypothesized that the effect of AEZS-108 on pituitary gonadotrophs may serve as an effective substitute for these agents in this clinical setting. Indeed, the median testosterone level during therapy was 12 ng/dL, well below castrate levels (Supplementary Table S1). Four of the patients only had one testosterone value measured. Of the remaining 14 patients, 3 had a decrease in testosterone, 7 had no change in testosterone and 4 had an increase in testosterone during therapy.

AEZS-108 showed signs of clinical activity, with 3 of the 18 evaluable patients experiencing a PSA PR by PSA Working Group Criteria and another 10 patients achieving PSA SD. In this heavily pretreated group of patients, this signal of activity is promising and efficacy will be further elucidated by the ongoing phase II portion of this study. We also demonstrated the feasibility of CTC capture using a slot filter. The structure of doxorubicin allows autofluorescence and we theorized that internalization of AEZS-108 could thus be visualized in captured CTCs following infusion. Our findings show that this is feasible and this study will be further developed in the phase II study to correlate the presence and degree of internalization with response. Previous groups have shown the change in CTC number reflected prognosis with a given therapy (27). We did not quantify CTCs in this phase I study, instead exploring their potential as a real-time pharmacodynamic biomarker with predictive value, though the absence of serial quantification is a limitation and will be done as part of the phase II study.

In summary, AEZS-108 is a tolerable agent with activity in men with taxane- and castration-resistant prostate cancer. The DLT consists of persistent neutropenia, which may warrant use of prophylactic colony-stimulating factors. The MTD and recommended dose for further study in this patient population is 210 mg/m² given intravenously every 3 weeks. CTCs captured on a microfilter demonstrate internalization of AEZS-108, a phenomenon that will be evaluated for predictive value. A single-arm, phase II study in men with refractory prostate cancer is ongoing. The efficacy of this agent in other tumors bearing LHRH receptors warrants exploration and a phase III trial in recurrent endometrial cancer and a phase II trial in advanced bladder cancer are ongoing.

Disclosure of Potential Conflicts of Interest

T. Dorff is a consultant/advisory board member for Astellas, Dendreon, Janssen, and Medivation and reports receiving speakers bureau honoraria from Bayer and Sanofi. D. Quinn is a consultant/advisory board member for Algeta, Amgen, Astellas, Bayer, Dendreon, Genentech, Janssen, Medivation, Millennium-Takeda, and Novartis and reports receiving speakers bureau honoraria from Medivation and Teva. Y. Tai has a patent for Membrane Filter for Capturing CTC, which is licensed to Cal Tech. J. Engel was an employee of and has ownership interest in Aeterna Zentaris. A. Schally reports receiving research support from Aeterna Zentaris and has a patent for Targeted Cytotoxic Anthracycline Analog, which is assigned to Tulane University. J. Pinski reports receiving speakers bureau honoraria from Aeterna Zentaris. No potential conflicts of interest were reported by the other authors.
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Writing, review, and/or revision of the manuscript: S.V. Liu, D.D. Tsao-Wei, S. Groshen, T.B. Dorff, D.I. Quinn, J. Engel, D. Hawes, A.V. Schally, J. Pinski

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