A resurgence of interest in clinical immunotherapy has generated a large number of methodologies to test a wide range of immune modulators and adoptive therapy techniques (1–5). Many immunotherapy strategies target the innate immune system to stimulate natural killer (NK), NKT, and T memory cells through the activation of dendritic cells via their constitutive receptors to foreign antigens (6–8). Many receptors are part of the toll-like receptor repertoire that recognize microbial surface antigens and nucleic acids (9, 10). In the proper environment, dendritic cell activation can lead to the inflammatory Th1 response that provides immediate mobilization of mature quiescent cells and stimulation of the adaptive immune response through presentation of antigen and costimulation to the naïve T-cell compartment (6).

Dendritic cells are the central players in the regulation of both innate and adaptive immune responses. Their careful manipulation may provide a successful intervention to change the balance from anergy and tolerance surrounding tumors to one of recognition and attack. The apparent recruitment of T-regulatory cells by tumors creates a physical and chemical barrier to the steady-state level of inflammatory cells and their cytokines, fulfilling their natural role of preventing autoimmune reactions throughout the body. The current goals in immunotherapy are to safely and stably activate the inflammatory response, whereas simultaneously weakening the immunosuppressive influence of T-regulatory cells within the tumor environment (11–12).

Many innate immunostimulators are currently in preclinical and clinical testing, representing a large number of the known ligands for the toll-like receptor repertoire. A novel protein from the Apicomplexa protozoan, *Eimeria* (13), a coccidian commonly infecting the intestine (14), was recently shown to be a potent stimulator of innate immunity inducing a Th1 type response that generates effective antitumor (15) and antiviral activity in mice (16, 17). This 19 kDa protein (*Eimeria* antigen, denoted as EA) represents the first class of innate immunostimulators from protozoa, with homologues appearing in various Apicomplexan protozoa, including *Toxoplasma* (18). The molecule is an activator of dendritic cells and is one of the most potent inducers of interleukin-12 (II-12) in mice,
where it acts through TLR-11 (18), yet it lacks any discernible toxicity in vivo, even at exceptionally high doses (15). A recombinant form of the *Eimeria* protein (rBBX-01) was produced and formulated for testing in this human phase I trial. Although the human gene for TLR-11 is truncated and believed to be nonfunctional, evidence is presented here that humans can respond to this protein over a broad range of concentrations.

During a research program to explore the mechanisms underlying the very low incidence of tumorigenesis in the small intestine, a highly immunostimulatory intestinal extract was partially purified and tested in humans under a previous IND. A significant partial response was observed using this extract in a patient with germ cell ovarian cancer, including a significant reduction in tumor burden and elimination of ascites, ultimately generating a dramatic improvement in quality of life (N.V. Dimitrov, personal communication).

Testing of the recombinant form of EA (rBBX-01) began with a single-dose pilot study in 12 patients at four dosages to show the initial safety of rBBX-01 (N.V. Dimitrov, personal communication). There were no toxicities observed in a wide spectrum of cancers in these initial patients, and thus, the safety of the initial multidose trial was established. The multidose testing (reported here) is composed of three phases: low doses, accelerated dose escalation, and high doses. Each was based on a 5-day course. The study was terminated when safety was established and sufficient pharmacokinetic information was obtained. The experience with rBBX-01 indicates that it has no local or systemic, acute or delayed toxicities. The pharmacokinetic results indicate that rBBX-01 behaves similarly to other proteinaceous drugs and can be reliably measured over several decades of plasma concentration. In the ovarian cancer setting, several patients showed reductions in the tumor marker CA125, correlating to plasma IL-12 elevations.

**Patients and Methods**

**Patients.** Between June 2005 and June 2006, 16 patients with incurable gynecologic malignancies were enrolled onto this phase I study at Washington University School of Medicine. The study was approved by the Washington University School of Medicine Human Research Protection Office (Institutional Review Board) prior to the commencement of patient accrual. Eligibility criteria included incurable, recurrent gynecologic malignancies, age >18 years, Gynecologic Oncology Group performance status ≤2, life expectancy ≥3 months, adequate hematologic, renal, and liver function, and no chemotherapy or radiotherapy within 4 weeks of enrollment. Exclusion criteria included allergy to penicillin, brain metastasis, uncontrolled intercurrent illness, and concurrent antiviral therapy.
Evaluation during treatment. Each patient underwent a physical examination before initiating therapy, at midstudy (day 15), and at end-of-study (day 30). Patients were observed for 6 h after each daily s.c. injection. Blood samples for complete blood counts, serum electrolytes, liver function tests, urea nitrogen and creatinine, and pharmacokinetics and pharmacodynamics were drawn just prior to treatment, 6 h post-injection, at midstudy, and at study end.

At day 30 patients were off-study unless they qualified for a second course of treatment, which was offered to patients with any evidence of response. Patient status was routinely monitored beyond this point because these patients were under continued care by the investigators. The National Cancer Institute Common Toxicity Criteria (v3.0) was used to assess toxicity. Plasma CA125 (when appropriate as a tumor marker) and clinical assessments were used to determine possible responses to treatment.

Drug preparation. rBBX-01 was supplied by Barros Research Institute, Holt, MI, as a solution for s.c. injection in 1.0 mL vials at a concentration of 5.0 mg/mL and in 2.0 mL vials at a concentration of 500 µg/mL. The protein was formulated in 3% human serum albumin for stabilization. Endotoxin levels were <1.0 units/mL.

Protocol design. The study consisted of three phases, all based on a regimen of five s.c. injections—one each day for 5 consecutive days. The first phase consisted of three low-dose levels; the second phase was an intrapatient accelerated titration that increased the dosage by 250 times, and the third phase consisted of two high-dose levels. The dose levels of the first phase were 0.85, 2.0, and 4.0 µg/m² per injection with three patients treated per level. The first patient in the dose acceleration schedule received doses of 4, 8, 16, 32, and 64 µg/m² on days 1 to 5, respectively. The second patient in the dose acceleration schedule received doses of 64, 128, 256, 512, and 1,024 µg/m² on days 1 to 5, respectively. The third phase of the study was composed of three patients receiving 1,000 µg/m² each day for 5 days and two patients receiving 2,000 µg/m² each for 5 days. The starting level of 1,000 µg/m² was determined after evaluation of the second accelerated patient.

The accelerated titration design followed the approach of intrapatient dose escalation (19). In brief, a stop/switch trigger point was defined prior to the start of the study. This consisted of (a) toxicity during the injection week or during the subsequent 30-day observation period, or (b) attainment of pharmacokinetic or pharmacodynamic thresholds. In the case of toxicities, two more patients would be enrolled at the same dosing. If two of three patients yielded toxicity, then the highest nontoxic dose in the most sensitive patient would be used as the starting dose for the third phase of the study. The decision tree checklist for the accelerated dosing is shown in Fig. 1.

Pharmacokinetics and pharmacodynamics. Blood samples for pharmacokinetic and pharmacodynamic analysis were obtained in heparinized tubes, which were centrifuged and the plasma removed and frozen. Samples were shipped to the Barros Research Institute for analysis, where both pharmacokinetic and pharmacodynamic measurements were determined with an in vitro bioassay and commercially available ELISA kits, respectively. Blood samples were drawn immediately prior to treatment and 6 h (nominally) post-injection. Preclinical experience in mice and hamsters, as well as pharmacokinetic measurements in a human pilot study (N.V. Dimitrov, personal communication), indicated peak drug levels near this time. The pilot study was used to show the safety of a single injection of rBBX-01 in cancer patients with various tumor types. Blood samples from selected patients were drawn at 0, 2, 4, 8, 24, and 48 h for pharmacokinetic analysis.

The pharmacokinetic analysis measured the induction of IL-12p70 release in primary cultures of murine dendritic cells. The details of the assay have been previously described (15). In brief, BALB/c mouse dendritic cells were isolated from spleens using the MiniMACS magnetic isolation system of Miltenyi Biotech with anti-CD11c+ microbeads. Cells, culture media, and cytokine agonists were added to microtiter plates with varying amounts of human plasma samples. Plasma was heat-treated at 55°C for 30 min prior to analysis to remove any unknown assay inhibitors. This treatment does not significantly affect the activity of rBBX-01 present in the plasma sample (the rBBX-01

**Table 1.** Patient characteristics, treatments, and responses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Cancer</th>
<th>Histology</th>
<th>No. of pretreatment regimens</th>
<th>Dose (µg/d)</th>
<th>Second course</th>
<th>CA125 decrease</th>
<th>IL-12 changes</th>
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<td>No¹</td>
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</table>

¹Administration of the second course followed the same dose and schedule as the first course.
²+, ++, +++; one, two, or more samples significantly above background, respectively; -, no change.
³CA125 not measured after the 30-d on-study period.
⁴CA125 did not decrease after subsequent chemotherapy.
⁵CA125 decreased after subsequent chemotherapy.

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The concentration for 50% effectiveness (ED$_{50}$) for rBBX-01 was measured with a standard ELISA for IL-12p70 after an overnight incubation. The concentration for 50% effectiveness (ED$_{50}$) for rBBX-01 is well established at 0.01 ng/mL in culture. Determining the level of drug in plasma samples consisted of measuring the activity generated in a dose-response curve analysis of the varying plasma dilutions. The response curve was fit to the sigmoidal Hill equation (20) and the 50% point was assigned to the known ED$_{50}$ value for EA. The concentration in undiluted plasma was then calculated.

The pharmacodynamic analysis consisted of measuring human IL-12 and IFN-$\gamma$ levels in plasma samples prior to, during, and following the rBBX-01 treatment. Plasma IL-12p70 concentrations were measured using a colorimetric sandwich-type ELISA (OptEIA Human IL-12p70 Set; BD PharMingen). Plasma IFN-$\gamma$ concentrations were also measured using a colorimetric sandwich-type ELISA (R&D Systems). Samples were assayed according to the instructions provided by the manufacturer. The sensitivity of both assays was ~5 pg/mL.

EC$_{50}$ assays. HaK hamster-transformed kidney epithelial cells were obtained from American Type Culture Collection and were propagated in DMEM/F12 culture medium supplemented with 10% FCS. Seven-week-old BALB/c male mice and 3- to 4-week-old male Golden Syrian hamsters were obtained from Harlan Industries. Spleens were harvested after euthanasia and used for dendritic cell/IL-12 release and NK cytotoxicity bioassays to determine sensitivity to the rBBX-01 protein. Animal care and treatment were conducted in accordance with the U.S. Laboratory Animal Welfare Act.

To determine the EC$_{50}$ in hamster cells, partially purified hamster spleen cells were cocultured with the hamster HaK tumor cell line in a standard NK cytotoxicity assay (15). Cytotoxicity was evaluated at various concentrations of rBBX-01 with various ratios of NK to target tumor cells. Effective cell killing was reached at a ratio of 60:1 and allowed a determination of the EC$_{50}$ for rBBX-01 in this system.

To determine the EC$_{50}$ in human cells, human peripheral blood mononuclear cells were isolated from buffy coat products obtained from a local branch of the American Red Cross. We used the well-documented synergism between IL-12 and IL-18 to induce IFN-$\gamma$ release, which was measured as described above.

**Results**

**Patients.** Sixteen patients received a total of 20 cycles (Table 1) of five daily s.c. injections of rBBX-01 over the three phases. Four patients (nos. 3, 5, 12, and 13) received a second 5-day cycle of treatment at 49, 49, 71, and 91 days, respectively, after the first treatment due to decreasing CA125. The mean age was 58 years (range, 35-76 years). All patients received prior chemotherapy and five patients also received prior radiotherapy. The mean number of previous chemotherapy regimens was six (range, 1-13 regimens). No concomitant antitumor therapy was allowed during the 30-day on-trial period. Patients were allowed nonsteroidal anti-inflammatory drugs on a pro re nata basis, but only patients 6 and 8 recorded any use of these drugs. Performance status was 0 to 1 for all participants. All patients were included in the determination of maximum tolerated dose and pharmacokinetic analysis.

**Toxicity.** All patients were evaluable for toxicity and no toxicity or discomfort was identified. There were no deaths on study. The regimen was extremely well tolerated with no nausea or vomiting. There was no change in hematologic indices or serum chemistries, liver, or renal function. Body temperature, blood pressure, and heart rates were all nominal during treatment.

**Preclinical studies.** The effective concentration for 50% activity (EC$_{50}$) was ~0.01 ng/mL in mouse cells in vitro. The minimum effective dose was ~5 ng/kg in mouse treatment protocols in vivo (15). These values were used to select the starting doses for the first phase of the human trial. Subsequent in vivo experiments using hamster and human cells have indicated that mice are unusually sensitive to rBBX-01. Hamster and human cells require ~1,000-fold higher concentrations to reach ED$_{50}$ levels. This is shown in Fig. 2.

The activation profile of hamster NK cells is shown in Fig. 2, where the Hill equation was fit to the data, yielding an EC$_{50}$ of 16 ng/mL. The mouse dendritic cell IL-12 release response from 13 stability assays of the 5.0 ng/mL dosage form covering a span of 3 years is shown for comparison (EC$_{50}$ = 0.009 ng/mL).

In human peripheral blood mononuclear cells, four of five cultures responded to rBBX-01 with a significant release of IFN-$\gamma$ generating a preliminary estimate of the EC$_{50}$. Although it is not clear if lymphocytes isolated from either human lymph nodes or spleen would respond in the same manner.
as human peripheral blood mononuclear cells, it allowed us to estimate an appropriate target concentration that may elicit an effect in human patients. An example of peripheral blood mononuclear cell sensitivity is given in Fig. 2, with an EC50 of 28 ng/mL, which is much closer to the hamster value than the mouse value. We used the accelerated titration in patients to determine the dose of rBBX-01 required to reach the vicinity of this EC50.

Pharmacokinetics. Blood samples taken during the single-dose pilot study (N.V. Dimitrov, personal communication) were generally too low to measure pharmacokinetics, however, two of the patients receiving 2 µg/m² yielded reliable estimates of rBBX-01 blood levels during the first 24 hours after injection. These are reported here to provide the necessary background for rBBX-01 preliminary pharmacokinetics. The kinetic profile of one of these patients is shown in Fig. 3A. The increase to peak levels and the decay from the blood is typical of other proteins and peptides given as subcutaneous treatments (e.g., see refs. 21, 22). Preliminary estimates of the pharmacokinetic variables from two individuals are as follows: volume of distribution, Vd = 0.72 L/kg; plasma half-life, t1/2 = 5.7 hours; maximum plasma concentration, Cmax = 0.03 ng/mL; and area under the concentration × time curve, AUC = 0.4 µg/L/h. The latter two are derived for the dose of 2.8 µg in a patient with a total weight of 58 kg.

By the end of the low-dose portion of this trial, we had obtained the in vitro result that humans are less sensitive to rBBX-01 than mice (see Fig. 2). This prompted the dose

![Graphs and Figures]

**Fig. 3.** Pharmacokinetics of rBBX-01 in human patients. **A,** plasma levels of rBBX-01 after an injection of 2.8 µg in a single patient from the single-dose pilot study (N.V. Dimitrov, personal communication). Plasma levels were determined with the in vitro dendritic cell bioassay. Points, mean of replicate samples; bars, SE. B, 6-h plasma levels in various patients spanning low doses to high doses: pilot study patient from (A); first dose escalation patient (no. 10; △); second dose escalation patient (no. 11; ■); points, averages for patients from the 1,000 and 2,000 µg/m² dose levels (nos. 12–16); bars, SE. Solid line, the best-fit power law equation with variables given in the fit equation. C, individual 0 and 6-h averages for the five 1,000 µg/m² courses administered to patient nos. 12 to 14. D, individual 0 and 6-h averages for the two 2,000 µg/m² courses administered to patients 15 and 16.
In the dose escalation (accelerated titration) phase, two patients were treated with intrapatient dose escalation to rapidly make the transition from the plasma levels targeted from the mouse data to the new levels deemed necessary for humans. The first patient received 4, 8, 16, 32, and 64 μg/m² doses during the course of the five-injection day. The second patient received 64, 128, 256, 512, and 1,024 μg/m² doses. These patients corresponded to 1A and 2A in the decision tree scheme, respectively (Fig. 1). Plasma Cₘₐₓ levels were determined in blood samples obtained from the first and second patients 6 hours post-administration of rBBX-01, and are shown in Fig. 3B as triangles and squares, respectively. The observed plasma levels scaled linearly with the dose levels, spanning approximately three orders of magnitude.

After transition to a high-dose conventional design, the plasma levels for the three patients treated at 1,000 μg/m²...
were followed throughout the week at hours 0 and 6 for each day of injection. The compilation of five courses in three patients is shown in Fig. 3C. Fairly consistent plasma levels of rBBX-01 were reached near the time of $C_{\text{max}}$ (6 hours) and some residual drug was present 24 hours later at time 0 for the subsequent dose. Two patients were treated with 2,000 µg/m², yielding higher mean plasma levels than patients receiving 1,000 µg/m² (Fig. 3D). The means of all 6-h plasma levels for each of the two high-dose groups are shown as the two upper points in Fig. 3B with SE bars barely visible. These continue the linear trend created by the accelerated titration of patients indicating that rBBX-01 is well-behaved and that predictable plasma levels of active drug could be achieved.

**Pharmacodynamics.** Plasma IL-12 levels were chosen as the primary pharmacodynamic marker at the beginning of the study because of the dramatic increase in plasma levels in the mouse (five orders of magnitude) after EA injection (15). For a similar reason, plasma IFN-γ was used as a secondary pharmacodynamic marker. In all patient plasma samples examined, IFN-γ levels were highly variable and either undetectable or did not change during treatment. Plasma IL-12 levels did not yield the large dynamic range previously

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**Fig. 5.** Pharmacodynamics of CA125 responses in human patients. Top, CA125 measurements in patient nos. 5, 6, 12, and 13, spanning pretreatment and posttreatment times (in weeks). Bottom left, the normalized composite of these patients, in which all responses were normalized to 100% of the maximum value reached during the period examined. The best-fit regression prior to the first rBBX-01 treatment is a third-order polynomial and the regression for posttreatment points is a second-order polynomial. The points include all data from patient nos. 5, 6, 12, and 13 with the exception of the rebound points after day 10 in patient 13. Bottom right, a composite of nonresponders, with all data normalized to the values at day 0 (first day of rBBX-01 injection). The regression line is given by a third-order polynomial fit (DCA, docetaxel + carboplatin + avastin; Gem/Dox, generic gemcitabine + pegylated liposomal doxorubicin; HK-272, Wyeth Pharmaceuticals oral Her-2 phase I experimental drug).
observed in the mouse, but did significantly change in some patients. Patients 5, 6, 12, and 13 exhibited reductions in CA125 (see below), and tended to show some increase in IL-12 levels at some time during the 5-day treatment period. This is summarized in Table 1.

Selected examples of plasma IL-12 levels from several patients receiving varying doses of rBBX-01 are shown in Fig. 4. These are shown in comparison to the large spike of IL-12 that occurs on the first day of injections in a mouse (Fig. 4A, note log scale; also, pretreatment plasma levels of IL-12p<0 are undetectable in mice). Unlike the mouse response, which produces ~90% of total IL-12 yield on day 1 of a five-day course, the human response was delayed until the end of the week using both the bovine extract (Fig. 4B) and the recombinant product in low and high doses (Fig. 4C and D).

Among those patients in the accelerated and high-dose phases, patients 10, 12, 13, and 16 exhibited modest increases in IL-12 but the timing of the increase was not stable across patients. These are shown in Fig. 4D. Patients 12 and 13, received a second course of treatment. These are indicated as 12B and 13B. Two trends that may be occurring are either a single elevation sometime during the week or minor elevations after each injection (e.g., patient 12B). In addition, the higher doses seem to result in elevations moving closer to the beginning of the week, which is more like the mouse response and less like the low-dose rBBX-01 response. In patients 1, 2, 7, 8, 11, 14, and 15 the plasma levels IL-12 exhibited either no change or no discernable pattern of change.

Antitumor response. The tumor marker, CA125, has been recommended as a valid method to monitor the extent and progress of several tumors, in particular, ovarian cancer (23–28). All patients were accessible for response at 30 days. Of 14 patients with ovarian, primary peritoneal, cervical, or endometrial cancer with elevated and increasing CA125 biomarkers at the start of treatment, 4 responded with decreased levels of CA125. One patient showed decreasing CA125 levels for 10 months and received no additional chemotherapy for 11 months following her last dosing with rBBX-01. In most of these cases, the decrease occurred a few weeks after completion of rBBX-01 treatment. This is shown individually and in composite in Fig. 5 (top and bottom left). In each case, week 0 represents a measurement just prior to the first course received by the patient. The general trend is that CA125 continues to increase until approximately week 5, then stabilizes and begins to decrease, which is also typical of various chemotherapy regimens. In the nonresponding cases (Fig. 5, bottom right), the trend is a continuous increase in CA125.

Discussion

This is the first reported clinical trial of the protozoan-derived, innate immunostimulator rBBX-01. The study was designed to assess safety and to determine the minimum effective dose required to reach plasma levels anticipated to be active in humans. The drug is well tolerated over a 1,000-fold range of doses, with no observable toxicity or discomfort. Pharmacokinetic analysis indicated a plasma concentration profile and clearance typical for subcutaneously injected proteins and peptides (21, 22). Limited pharmacodynamic analysis revealed increases in IL-12 in some patients during the week of injections, which tended to correlate with delayed reductions in CA125 following the 30-day time frame.

In many patients, the plasma IL-12 was elevated prior to dosing with rBBX-01, probably indicative of a disease-perturbed immune status. In a small study by Kovacs et al., the level of IL-12 was 3-fold higher in cancer patients than controls (29). In patients with highly elevated IL-12, rBBX-01 tends to reduce this level during the week of therapy, usually following a spike in IL-12. The cause of this response is not known. Weak IL-12 responses were detected in a few patients receiving very low doses of rBBX-01. There were also CA125 reductions in two low-dose patients. This suggests that there is a broad spectrum of responsiveness to this innate immune stimulator, perhaps due to genetic differences in receptor expression. Future work will benefit from the development of a screening test to determine individual patient responses.

The exact tumoricidal mechanism of action of rBBX-01 has not been elucidated; however, the marked increase in serum IL-12 in mice suggests that this cytokine may play a role. IL-12 has been shown to have antitumor activity in a wide variety of murine tumor models (30) and its presence at the tumor site is critical for tumor regression. IL-12 inhibits angiogenesis in many tumors (31) and is an effective stimulus for IFN-γ production, which can markedly enhance STAT-1 expression within immune effector cells and tumor cells. The use of cytokines in clinical trials can be problematic due to grade 3 and 4 toxicities. These toxicities include nausea and vomiting, fever, fatigue, and neutropenia (32). None of these side effects were seen in this study. rBBX-01 may therefore provide an alternative method of delivering IL-12 to the tumor without associated toxicities.

The use of CA125 as a measure of rBBX-01 activity is consistent with clinical experiences for this tumor marker. Many patients with recurrent ovarian cancer will not have clinically or radiographically measurable disease; however, >90% of patients have an elevated CA125. The Gynecologic Cancer Intergroup simplified CA125 response criteria (27), and showed better response assessment in second-line treatment with topotecan or paclitaxel plus carboplatin in patients with ovarian carcinoma (24) compared with the Response Evaluation Criteria in Solid Tumors Group criteria (28). In addition, CA125 levels can continue to increase initially in the 30 days after chemotherapy prior to a decrease in levels. This was seen in nearly 50% of responders who received pegylated liposomal doxorubicin for recurrent ovarian cancer (23). This pattern was typical of the responders in our study with rBBX-01.

The prior experience with rBBX-01 in the murine system (15) highlights the large discrepancies that can occur in the biological responses of two species, resulting in misleading guidance for the establishment of starting doses in human trials. These discrepancies can lead to the failure to pursue promising therapies, as well as offer inadequate effectiveness to patient volunteers. The identification of a suitable animal model, such as hamsters in this study, allows proper dosing targets in early human studies. Once identified, these targets can be rapidly reached by incorporating an aggressive dose escalation within patient groups, minimizing the number of patients required.
In conclusion, the innate immunostimulator, rBBX-01, is very well tolerated in subjects with gynecologic malignancies and no short-term side effects at doses up to 2,000 µg/m². This phase I study did not identify any objective measurable tumor responses after one course of treatment. However, four patients showed a decrease in CA125 after 30 days prior to additional cytotoxic chemotherapy. The correlation of plasma IL-12 and tumor markers predictive of response was limited due to the small sample size in this study. There was a decrease in CA125 noted in ~30% (4 of 14) women with pretreatment-elevated biomarkers, suggesting that rBBX-01 has biological activity. One patient experienced a 77% total decline in CA125 (from 13,297 to 3,066), 9 months after the first cycle and 6 months after the second cycle of treatment. The safety of rBBX-01 and the suggestion of antitumor activity in ovarian cancer makes the use of this agent in combination with cytotoxic therapies an attractive option for future phase I/II studies. Preclinical multicourse therapy in hamsters has indicated substantial improvement in efficacy at doses equivalent to the 1 to 2 mg/m² doses used here in humans. The safety of multicourse rBBX-01 therapy in humans, at doses of 1 to 4 mg/m², will be explored in that regard.

Disclosure of Potential Conflicts of Interest

C. Aylsworth and D. Juckett may receive future income from a pending patent on the active ingredient in rBBX-01.
Phase I Study and Preliminary Pharmacology of the Novel Innate Immune Modulator rBBX-01 in Gynecologic Cancers

Janet S. Rader, Charles F. Aylsworth, David A. Juckett, et al.


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