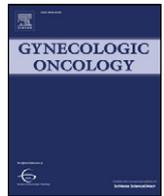




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A phase II trial of intraperitoneal EGEN-001, an IL-12 plasmid formulated with PEG–PEI–cholesterol lipopolymer in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: A Gynecologic Oncology Group study[☆]

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HIGHLIGHTS

- Twenty eligible patients with recurrent ovarian cancer were treated with EGEN-001.
- There were no tumor responses, and 3 patients were successful by 6-month EFS.
- More frequent toxicities included nausea, vomiting, pain, fatigue, and anemia.

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ABSTRACT

Objective. The purpose of this phase II trial was to evaluate the toxicity and antitumor activity of EGEN-001 in platinum resistant recurrent ovarian cancer.

Methods. Eligible patients had weekly IP infusion of EGEN-001 at a dose of 24 mg/m². Toxicity and antitumor activity were evaluated using CTCAE and RESIST criteria, respectively. Co-primary endpoints were tumor response and survival without progression (PFS) for at least 6 months. Survival without progression before going onto a subsequent therapy (EFS) for at least six months was also considered.

Results. A total of 58 EGEN-001 cycles were administered to 20/22 enrolled patients (median 2 cycles, range 1–9). The most frequently associated adverse events related specifically to EGEN-001 treatment were grade 1/2 fatigue, fever, chills, abdominal pain, nausea, vomiting, anemia, thrombocytopenia, and leukopenia. Three of 20 EGEN-001 treated patients evaluable for toxicity elected to withdraw from the study motivated in part by grade 1 treatment related toxicities. There were no patients with partial or complete response (0%; 90% CI 0–10.9%). Seven (35%) of 16 patients evaluable for response had stable disease, and 9 (45%) had progressive disease. Six (30%) patients had a PFS of greater than six months, although three had gone off study and onto other therapies before six months. The estimated six-month EFS was 15%. The median PFS and OS were 2.89 and 9.17 months, respectively.

Conclusion. EGEN-001 at the dose and schedule evaluated was associated with some but limited activity and was seemingly less tolerated in platinum resistant recurrent ovarian cancer patients.

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Introduction

Immunocytokine based therapies for patients with ovarian cancer, a disease in need of new therapeutic paradigms, have been the subject of intense investigation. Interferon-alpha (IFN- α), IFN- γ , IL-2 and IL-12 are the predominant cytokines with proven activity in preclinical models of ovarian carcinoma [1]. In general, IL-12 is one of the most active immunocytokines due to its potent immune-modulatory properties and ability to activate the cascade of cellular and biochemical events leading to a robust local and systemic immune response to cancer. These events include natural killer cell proliferation and activation, IFN- γ secretion, T-helper cell differentiation and development of cytotoxic CD8 + T-cell responses, subsequently leading to tumor suppression [2]. In addition, IL-12 also inhibits the process of tumor neovascularization which leads to tumor death from starvation [3]. These features make IL-12 distinct from other cytokines due to its ability to activate both innate and adaptive immunity and to inhibit tumor angiogenesis. A phase II trial evaluating recombinant human interleukin-12 (rhIL-12) administered by weekly intraperitoneal (IP) injection was conducted in ovarian cancer patients with persistent low volume disease after primary therapy [4]. The results of this trial were similar to that noted in studies evaluating rhIL-12 in other solid tumors wherein limited responses and moderate toxicity were noted. This has led investigators to explore alternative means of IL-12 delivery.

EGEN-001 is a novel IL-12 based immunotherapeutic agent that is comprised of a human IL-12 expressing plasmid that encodes for functional IL-12 protein, and a synthetic DNA delivery system polyethyleneglycol–polyethyleneimine–cholesterol (PPC) that facilitates plasmid delivery in-vivo [5,6]. This formulation is designed for direct injection into solid tumors or into the abdominal cavity with disseminated tumors to express immunocytokine IL-12 at the injection site, producing an expanded immune response against tumor cells at the injection site and against tumor metastasis at distant sites. Preclinical studies by Fewell et al. have demonstrated biologic and antitumor activity of a murine IL-12 expressing plasmid formulated with PPC (pmIL-12/PPC) when administered IP in an in vivo ID8 cell model of ovarian cancer [7]. Specifically, peak levels of mIL-12 were noted 1 day after IP injection and declined to near baseline by 7 days. Levels of murine IFN- γ peaked 3 days after mIL-12/PPC administration and declined to 25% of peak levels by 7 days. There was a significant reduction in murine VEGF levels in ascites samples that also lasted for about 1 week. A PCR array of ascites and tumor samples in these experiments analyzing 84 genes involved in immune activation demonstrated a general shift towards a Th1 type immune response. Experiments analyzing the biologic effects of multiple IP injections demonstrated that expression levels of mIL-12 and IFN- γ similar to that noted with a single injection could be achieved. Additional in vivo preclinical experiments evaluated 4-weekly IP injections of pmIL-12/PPC at dosages ranging from 10 to 250 μ g alone and up to nine weekly IP injections of pmIL-12/PPC at dosage of 100 μ g given in combination with paclitaxel/carboplatin. Survival in these ovarian cancer animal models was significantly improved with pmIL-12/PPC monotherapy when dosages exceeded 100 μ g and with the combination pmIL-12/PPC and chemotherapy approach.

Subsequent phase I trials have demonstrated the feasibility and safety of EGEN-001 administered IP alone or in combination with chemotherapy in patients with recurrent ovarian cancer [8,9]. In these trials, patients were treated with EGEN-001 administered IP weekly or every 10 days for up to 8 treatments at dosages up to 24 mg/m². Common side effects included low-grade fever and abdominal pain in both trials and disease responses and/or a reduction in serum CA-125 levels were observed in some patients.

Given these preclinical and early-phase clinical trial findings, we sought to evaluate in an expanded phase II trial the toxicity profile and antitumor activity of EGEN-001 administered IP in patients with platinum resistant recurrent ovarian, fallopian tube or primary peritoneal cancer.

Methods

Eligibility criteria

Patients were required to have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma based upon prior or recent pathologic analysis and current imaging studies. Patients were required to have received at least one prior platinum regimen and could have received one additional cytotoxic regimen. Patients who received only one prior platinum regimen must have had progressive disease during primary treatment, had persistent disease at the completion of primary treatment, or had a platinum-free interval of less than 12 months.

All patients were required to have measurable disease on CT scan as defined by RECIST 1.1. Patients could have received up to two prior chemotherapy regimens. Patients were also required to have a PS of 0–2 and adequate organ function defined as an absolute neutrophil count (ANC) greater than or equal to 1500/ μ l, platelets greater than or equal to 100,000/ μ l, creatinine less than or equal to 1.5 \times institutional upper limit normal (ULN) or calculated creatinine clearance of greater than or equal to 50 ml/min, bilirubin less than or equal to 1.5 \times ULN, SGOT (AST) less than or equal to 3 \times ULN, alkaline phosphatase less than or equal to 2.5 \times ULN and neuropathy (sensory and motor) less than or equal to CTCAE grade 1.

Patients were required to be at age 18 or greater. Patients with other malignancies other than non-melanoma skin cancer or early stage endometrial cancer who did not have stage not greater than I-B, more than superficial myometrial invasion, vascular or lymphatic invasion, or poorly differentiated subtypes (papillary serous, clear cell or other FIGO grade 3 lesions) were ineligible for the study. Patients who had received radiation to the abdominal cavity or chemotherapy for non-gynecologic cancers within the last three years; with serious uncontrolled medical conditions, active infections, or abdominal surgery other than placement of an IP port; and who were pregnant or breastfeeding were also excluded from the study.

IRB and IBC approvals were obtained at each participating institution and all eligible patients were required to sign informed consent.

Treatment plan

Eligible patients had placement of an IP catheter according to GOG guidelines (<https://gogmember.gog.org/manuals/pdf/surgman.pdf>) greater than one week prior to the scheduled EGEN-001 dosing if they had no pre-existing IP catheter. Prior to each infusion of EGEN-001, the IP catheter was flushed with approximately 25 ml of saline to check for IP catheter patency. EGEN-001 was reconstituted in 12 ml SWFI prior to infusion to achieve a dose of 24 mg/m² and then infused via gravity through the IP catheter as quickly as the patient tolerated within a two hour time period. The IP catheter was flushed with approximately 200 ml of saline upon completion of EGEN-001 administration. The treatment was given on an outpatient basis and was repeated once every week (four weeks = 1 cycle). Patients were not allowed to receive white blood cell growth factors but were instructed to use acetaminophen or ibuprofen as needed for fever or pain. Patients continued therapy until disease progression or adverse effects prohibited further therapy or a patient elected to withdraw from the study.

Assessment for toxicity and treatment modification

All patients who received at least one dose of EGEN-001 were evaluable for toxicity. Patients were assessed for adverse effects utilizing NCI CTC for Adverse Events (version 4.0) pre-treatment and then weekly with history and physical and laboratory tests (CBC with differential, platelets, electrolytes, and liver function tests). Attribution to treatment or other causes was assigned to all experienced adverse events by clinical investigators. Subsequent cycles of EGEN-001 therapy were

not to be administered until the ANC was ≥ 1500 cells/ μl , the platelet count was $\geq 100,000/\mu\text{l}$, and all non-hematologic toxicity had recovered to grade 1 or less.

Delay in further treatment and reduction of the EGEN-001 dose to 18 mg/m² was required for the first occurrence of febrile neutropenia, documented grade 4 neutropenia persisting \geq seven days, grade 4 thrombocytopenia; grade 2 or greater neuropathy, grade 2 or greater renal toxicity, grade 3 or greater hepatic toxicity, grade 3 gastrointestinal symptoms lasting greater than 24 h in spite of optimal medical management; or other non-hematologic toxicities with an impact on organ function of grade 2 or greater. Patients who failed to recover from any of the aforementioned toxicities within a two-week delay were removed from the study.

Assessment for clinical efficacy

Radiographic imaging (CT scan or MRI) was obtained within 28 days of initial treatment and then after every other cycle to assess for clinical response. Response was evaluated by comparing pre and post imaging target and non-target lesions using the international criteria proposed by RECIST v.1.1 guidelines. The presence of new lesions was an indication of progressive disease. Only those patients who had received at least 1 cycle of therapy and had their disease re-evaluated were considered evaluable for response. Patients with global deterioration of health requiring discontinuation of treatment, without objective evidence of disease progression at the time, were reported as symptomatic deterioration.

CA125 was also assessed pre- and post-EGEN-001 treatment but was not used to assess response. CA125 levels elevated above normal limits were required to normalize in patients considered to have a complete response.

Statistical considerations

The primary objective of the study was to evaluate the efficacy of the regimen through the frequency of patients with objective tumor responses and the frequency who survived progression-free (PFS) for at least six months. In addition, six-month event free survival (EFS), defined as the six-month PFS without going onto a subsequent therapy, was also evaluated. Activity on either response or six-month PFS was considered indicative of worthiness of further investigation.

The null hypothesis relating to uninteresting levels of activity was determined from an analysis of a historical dataset based on a similar population of patients where the levels of activity of the study drugs were believed to be inactive to modestly active. The null hypothesis jointly specified the probability of a patient experiencing a tumor response to less than or equal to 10% and the probability of a patient being six-month PFS to less than or equal to 15% (i.e. $H_0: p_r \leq 0.10$ and $p_s \leq 0.15$). Clinically significant differences were a 20% increase in the probability of six-month PFS or a 15% increase in the probability of response (i.e. $H_1: p_r \geq 0.25$ or $p_s \geq 0.35$).

The null hypothesis was evaluated by the data with a flexible method provided by Sill et al., which is a two-stage design used to limit patient exposure to inactive regimens [10]. The targeted accrual for the first stage was 26 patients but was allowed to deviate for administrative purposes. If 20 patients were accrued, the critical value for the number of patients with responses was one and the critical value for the number of patients who were six-month PFS was four. The cumulative targeted accrual for the second stage would have been 53 and was allowed to deviate. If 53 patients were accrued, the critical value for the number of patients with responses was eight and the critical value for the number of patients who were six-month PFS was 12.

The goal of the design was to limit the expected probabilities of type I and II errors to approximately 10% under the assumed accrual ranges of 22 to 29 (stage 1) and 49 to 56 (cumulatively after stage 2). Using the method of Sill et al. [10], the realized type I error at the end of

stage two would have been about 11.2 to 9.3%, depending on the level of association between response and six-month EFS. The expected probability of early termination was likely between 33% and 38%, depending on the level of association between the two variables. Had the study accrued 53 patients in the second stage, the study would have had 90–93% power of detecting a clinically significant effect, depending on the level of association between the primary endpoints.

Results

Patient characteristics

Twenty-two eligible patients were enrolled in this trial from November of 2010 until January of 2013. Two patients had complications with their IP ports and did not receive treatment. Twenty patients were treated per protocol. Characteristics for treated patients are listed in Table 1. The median age of enrolled patients was 57 years. The majority of the patients were Caucasian, had platinum resistant serous ovarian cancer, and had received two prior chemotherapy regimens.

A total of 58 EGEN-001 cycles were administered to the 20 treated patients with a median of 2 cycles and a range of 1–9. Six patients received 1 cycle or less of EGEN-001 therapy due to either adverse events or disease progression. One patient had a port complication after two EGEN-001 cycles that contributed to withdrawal from the study. The total dose of EGEN administered to evaluable patients in this study was 9026.56 mg. The total dose per patient ranged from 36 to 1550 mg (median total dose was 299 mg).

Adverse events

Adverse events experienced by the 20 evaluable EGEN-001 treated patients that were at least possibly related to EGEN-001 are listed in Table 2. The most frequently experienced clinical side effects were fatigue (11), fever (4), chills (4), abdominal pain (7), nausea (14) and vomiting (7). The most frequently experienced laboratory effects were anemia (11), thrombocytopenia (7), and leukopenia (5). The majority of clinical and laboratory adverse events were grade 1/2 in nature, transient and medically manageable. Grade 3 adverse events deemed at least possibly related to EGEN-001 included nausea and vomiting (2), anemia (1), and decreased lymphocyte count (1). No patients had

Table 1
Patient characteristics.

Characteristic	Category	No. of cases	% of cases
Age	40–49	1	5.0
	50–59	12	60.0
	60–69	5	25.0
	70–79	2	10.0
Race	African American	1	5.0
	Hispanic	1	5.0
	White	18	90.0
Performance status	0	11	55.0
	1	8	40.0
	2	1	5.0
Site of disease	Ovary	19	95.0
	Peritoneum	1	5.0
Cell type	Endometrioid	1	5.0
	Serous	18	90.0
	Adenocarcinoma, NOS	1	5.0
Prior chemotherapy	1 prior regimen	6	30.0
	2 prior regimens	14	70.0
Prior radiation	No	20	100.0
Prior immunotherapy	No	19	95.0
	Yes	1	5.0
Prior surgery	Yes	20	100.0
Platinum sensitivity	Platinum resistant	13	65.0
	Platinum sensitive	7	35.0
Prior platinum regimens	1 prior regimen	10	50.0
	2 prior regimens	10	50.0

Table 2
Adverse events deemed at least “possibly” related to EGEN-001 treatment. A) Clinical. B) Laboratory.

AE category	0	1	2	3	4	5	Total
A)							
Ear and labyrinth	18	1	1	0	0	0	20
Eye	18	2	0	0	0	0	20
Nausea	6	10	3	1	0	0	20
Vomiting	13	6	0	1	0	0	20
Abdominal pain	13	4	1	2	0	0	20
Other GI	12	6	2	0	0	0	20
Fever	16	3	1	0	0	0	20
Chills	16	4	0	0	0	0	20
Fatigue	9	7	4	0	0	0	20
General, NOS	15	1	4	0	0	0	20
Administrative site	17	1	2	0	0	0	20
Infections/infestations	19	0	1	0	0	0	20
Anorexia	17	3	0	0	0	0	20
Dehydration	18	0	2	0	0	0	20
Musculoskeletal/connective tissue	17	2	1	0	0	0	20
Peripheral sensory neuropathy	17	2	1	0	0	0	20
Other nervous system	17	3	0	0	0	0	20
Psychiatric	17	3	0	0	0	0	20
Reproductive/breast	19	1	0	0	0	0	20
Respiratory/thoracic/mediastinal	18	1	1	0	0	0	20
Skin/subcutaneous	16	4	0	0	0	0	20
B)							
Leukopenia	15	3	2	0	0	0	20
Lymphopenia	18	0	1	1	0	0	20
Neutropenia	15	5	0	0	0	0	20
Thrombocytopenia	13	6	1	0	0	0	20
Anemia	9	5	5	1	0	0	20
Hyponatremia	19	1	0	0	0	0	20
Elevated Creatinine	18	1	1	0	0	0	20
Hyperglycemia	19	1	0	0	0	0	20
Hypomagnesemia	18	2	0	0	0	0	20
Hypoalbuminemia	19	1	0	0	0	0	20
Elevated alanine aminotransferase	19	0	1	0	0	0	20
Elevated alkaline phosphatase	18	2	0	0	0	0	20
Elevated aspartate aminotransferase	18	1	1	0	0	0	20
Elevated GGT	19	0	1	0	0	0	20
Elevated bilirubin	19	0	1	0	0	0	20

febrile neutropenia. Five patients had a dose reduction for non-hematologic grade 1/2 adverse events. Many patients had adverse events which were attributed to their disease (data not shown).

Of the 20 EGEN-001 treated patients evaluable for toxicity, one patient went off study for a grade 2 increase in creatinine that was deemed “possibly” related to EGEN-001. Three other patients elected to withdraw from the study motivated in part by treatment related toxicities. One patient withdrew after experiencing grade 1 abdominal pain after 1 cycle of EGEN-001. Another patient withdrew after 3 cycles of EGEN-001 after experiencing grade 1 neuropathy and dyspnea when talking. Another patient withdrew for unacceptable nonspecific grade 1 side effects related to anemia and decreased WBC experienced during cycle 2 of treatment.

Clinical efficacy

Four of the 20 EGEN-001 treated patients were indeterminate for response since follow-up tumor measurements were not provided. Specifically, one patient died due to rapidly progressive disease soon after initiating EGEN-001 treatment. Three other patients withdrew without providing follow-up tumor measurements for symptoms of grade 1 abdominal pain, for symptoms of a small bowel obstruction, or for clinically progressive disease, respectively, after receiving 1 or 2 cycles of EGEN-001.

Of the 16 patients evaluable for response, seven (35%) had stable disease, and nine (45%) had progressive disease. The estimated probability of response is 0% (90% one-sided CI is 0–10.9%). PFS, EFS and OS are depicted in Fig. 1. Six (30%) patients had a PFS of greater than six

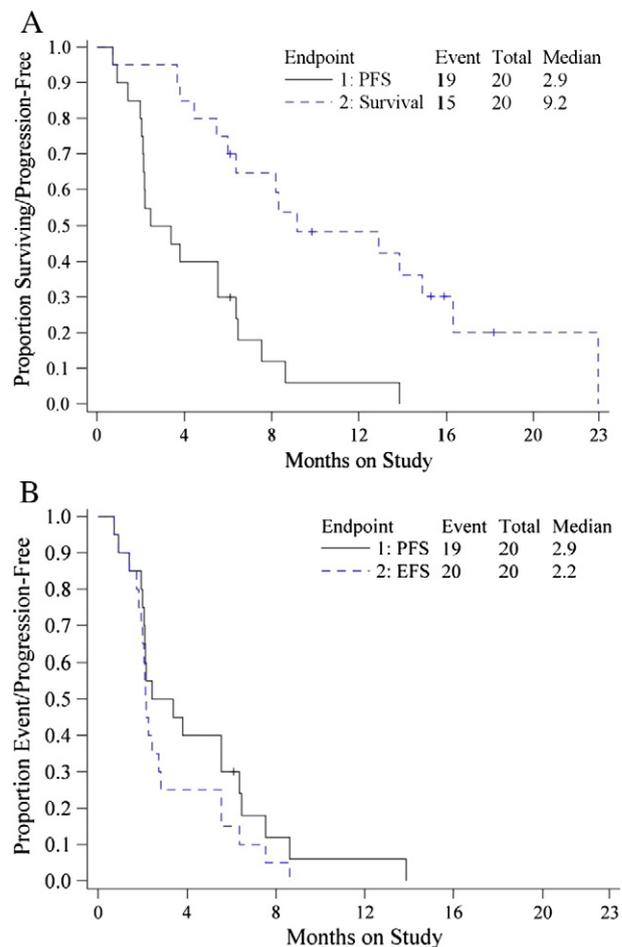


Fig. 1. Kaplan–Meier plots of (A) progression-free (PFS) and overall survival, and (B) Event-Free Survival (EFS) and Event-Free Survival (EFS). The endpoints for EFS are death, progression, or beginning a subsequent therapy.

months, although three had gone off study and onto other therapies before six months. The estimated six-month EFS was 15% (90% CI two-sided was 4.2–34.4%). The median PFS was 2.89 months, the median EFS was 2.15 months, and the median OS was 9.17 months.

Discussion

In the initial phase I monotherapy study, EGEN-001 was administered IP to 13 patients with platinum resistant recurrent ovarian cancer at dosages ranging from 0.6 mg/m² to 24 mg/m² once every week for four weeks [8]. The most frequent reported adverse events were low grade fever (69.2%) and abdominal pain (53.8%), which subsided within 24 h after the treatment. One patient in the 24 mg/m² cohort experienced a possibly reagent associated grade 3 peritonitis. The maximum tolerated dose (MTD) was not identified. Four patients (31%) were noted to have stable disease and nine (69%) were noted to have progressive disease five weeks after the last dose of study drug. CA-125 levels decreased or remained stable in six of the 13 treated patients at the five-week follow-up visit. All evaluable patients had detectable levels of plasmid DNA (range 46,430 to 418,084,000 copies/20 μl) in the peritoneal fluid at each study visit after EGEN-001 treatment. Plasmid levels were mostly detectable in the peritoneal fluid as compared to blood samples, suggesting that the EGEN-001 distribution was localized primarily within the peritoneal cavity. Significant increases in IFN-γ levels, a powerful mediator of IL-12 activity, were observed in the peritoneal fluid of every EGEN-001-treated patient.

In the subsequent phase 1A study, the safety and tolerability of EGEN-001 at escalating doses (12 mg/m², 18 mg/m² and 24 mg/m²) were assessed in combination with intravenous carboplatin (AUC 5) and docetaxel (75 mg/m²) in platinum-sensitive recurrent ovarian cancer patients [9]. In this study, a subcutaneous implanted IP catheter rather than a percutaneous one was used for EGEN-001 IP infusion to minimize the incidence of peritonitis observed in the initial phase I study. EGEN-001 was infused every 10–11 days for 4 cycles in combination with docetaxel and carboplatin at three-week intervals for a planned 6 cycles. In the second stage of the trial the MTD from the dose escalation study (24 mg/m²) was examined for up to eight treatment cycles administered every 10–11 days in combination with chemotherapy at three-week intervals for a planned 6 cycles. In general, the combination treatment was well tolerated at all EGEN-001 doses and an MTD was not identified. Common treatment-related adverse events included low grade fever and abdominal pain, which subsided with the use of analgesics within 24 h after the treatment. Grade 1 hypotension was reported in two patients and a grade 3 hypotension was reported in a third patient, which was managed by fluid infusion; all episodes occurred at the 24 mg/m² dose. The best overall antitumor response (17% CR, 33% PR, 42% SD and 8% PD) was typical of the patient population enrolled for the study. Post-treatment increases in cytokine (IFN- γ and TNF- α) levels were detected mainly in peritoneal fluid although some serum samples contained small increases in TNF- α .

In aggregate these two initial studies demonstrated the feasibility and safety of IP administration of EGEN-001 in patients with recurrent ovarian cancer alone and in combination with chemotherapy. The purpose of the current study was to assess the safety and efficacy of EGEN-001 monotherapy at the 24 mg/m² dose administered IP on a weekly basis in a larger population of platinum-resistant recurrent ovarian cancer patients. The 24 mg/m² dose was selected for this study because it was the highest EGEN-001 dose tested without dose limiting toxicity in the previous clinical trials. The activity noted in the current trial was similar to that noted in the initial phase I trial conducted in platinum resistant ovarian cancer patients. Specifically, the best overall response noted was stable disease, which occurred in seven patients (35%). No partial or complete responses were noted. Though six patients (30%) had a PFS of greater than six months which met the initial study goals, three of these patients withdrew from the study without obvious disease progression and went on to additional therapies prior to the six-month evaluation point. Thus, the six-month EFS was 15%. The lack of objective responses and the few patients who achieved six-month PFS without receiving additional therapy before that time point suggest that EGEN-001 has some but limited antitumor activity in this platinum resistant recurrent ovarian cancer patient population. The fact that only 30% of patients received 1 cycle or less of EGEN-001 may also have limited the ability to assess the true antitumor activity of this agent in this trial.

EGEN-001 specific toxicity in the current study was largely similar to that noted in the earlier phase I studies. However, there was one patient who experienced a grade 2 elevation in creatinine who was removed from the study and several other patients that experienced toxicities that motivated them to withdraw from the study. Of note, in contradistinction to prior phase I trials, all patients in the current trial were treated at the 24 mg/m² dose. This in addition to other disease related symptoms may have impacted the ability of this specific group of platinum resistant recurrent ovarian cancer patients to tolerate EGEN-001 over a greater number of cycles than that administered in earlier phase I trials and to a higher percentage of patients withdrawing from this trial for toxicity related symptoms compared to that noted in prior GOG trials in this patient population.

A phase I trial of EGEN-001 in combination with liposomal doxorubicin was initiated soon after initiation of this phase II monotherapy trial and accrual is in progress (ClinicalTrials.gov Identifier NCT01489371). The beneficial effects of doxorubicin in combination with IL-12 or

other immunostimulatory cytokines have been demonstrated in several tumor models [11–14]. Combination approaches involving immune modulating agents and chemotherapeutic drugs are gaining recognition based on recent preclinical and clinical studies [15,16]. Doxorubicin is of particular interest due to its ability to modulate the immune system in various ways including modulation of macrophage and natural killer cells and impairment of immune suppressing cells [17–20].

In conclusion, EGEN-001 in the dose and schedule evaluated in this trial demonstrated some but limited activity and was seemingly less tolerated in this group of platinum resistant recurrent ovarian cancer patients. The results of the ongoing phase I trial of EGEN-001 in combination with liposomal doxorubicin will provide key additional insights into how best to proceed with the development of EGEN-001 in the context of ovarian cancer. In addition, it may also be prudent to examine the status of patient's immune system on treatment outcome to fully understand the impact of IL-12 based therapy in ovarian cancer patients. A systematic analysis of the impact of the T-cell repertoire and lymphocyte compartments (e.g., CD4+, CD8+ T cells) on treatment outcome could help identify a subset of ovarian cancer patients potentially more responsive to IL-12 immunotherapy.

Conflict of interest statement

The co-authors have no conflicts of interest to declare.

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