A Phase I Study of Intraperitoneal EGEN-001 (IL-12 Plasmid Formulated with PEG-PEI- Cholesterol Lipopolymer) Administered in Combination with Pegylated Liposomal Doxorubicin in Patients with Recurrent or Persistent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer: an NRG/GOG Study

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Abstract

Background: EGEN-001 is a novel immunotherapeutic agent designed to treat cancer by enhancing the patient's immune system. EGEN-001 comprises a human IL-12 plasmid that encodes for functional IL-12 and a synthetic DNA delivery system polyethyleneglycol-polyethyleneimine-cholesterol that facilitates plasmid delivery into cells. Intraperitoneal (ip) injection of EGEN-001 is associated with increases in IL-12 levels and its downstream cytokines in the tumor environment without a significant increase in systemic circulation. The study's purpose was to assess safety and efficacy of escalating doses of EGEN-001 with pegylated liposomal doxorubicin (PLD) in patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancers (EOC).

Methods: Patient eligibility criteria: Females age ≥ 18 years with persistent or recurrent EOC. Patients were not required to have measurable disease and could have a biochemical recurrence; must have had one prior platinum-based chemotherapeutic regimen and up to two additional cytotoxic regimens; and have adequate organ function. The trial was a standard 3 + 3 phase I dose escalation with patients receiving PLD every 28 days and EGEN-001 ip on days 1, 8, 15, and 22 of a 28 day cycle (table 1). Cycles were repeated every 28 days until disease progression.

Results: Sixteen evaluable patients enrolled on trial from 9/2012-7/2012. No dose limiting toxicities (DLTs) were found during cycle one of each dose level. The adverse side effects were as follows: 4 grade 3 anemia; 2 grade 3 abdominal pain; 7 grade 3 neutropenia and 2 grade 4 neutropenia. There were minimal side effects of fever, flu-like symptoms, and infusion or injection site reactions. A clinical benefit of 57.1% (PR=21.4%; SD=35.7%) was found in the 14 patients with measurable disease. The highest number of partial responses were found at dose level 3 (28.6%) along with stable disease at 57.1%. The maximum tolerated dose was not achieved. Translational studies are ongoing.

Conclusions: EGEN-001 in combination with PLD has clinical benefit in recurrent or persistent EOC and warrants further investigation with escalating doses of EGEN-001. NCT#01489371

Background

- Ovarian Cancer is the most lethal of the gynecological malignancies. Generally second line and third therapies are ineffective and toxic.
- EGEN-001is a novel immunotherapeutic agent that is designed to treat cancer by enhancing the patient's immune system.
- EGEN-001 comprises a human IL-12 plasmid that encodes for functional IL-12 protein, and a synthetic DNA delivery system polyethyleneglycol-polyethlyeneimine-cholesterol (PPC) that facilitates plasmid delivery into cells *in vivo*.
- EGEN-001 is efficiently taken up by tumor and non-tumor cells and high concentrations of biologically active IL-12 are achieved in the tumor environment for several days without significant increases in systemic circulation.
- EGEN-001 activates innate and acquired immunity and inhibits ~~ion of~~ tumor angiogenesis.

Objectives

- **To determine the maximum tolerated dose and dose limiting toxicities of EGEN-001 when administered in combination with pegylated liposomal doxorubicin in women with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer.**
- **The secondary objective was to estimate the objective response rate (complete and partial) in patients with measurable disease.**

Methods

Eligibility Criteria: Females ≥18 years with persistent or recurrent epithelial ovarian cancer
May have biochemical recurrence or clinically evident measurable or non-measurable disease
Adequate hematologic, renal, hepatic, cardiac, and neurologic function
Must have had one prior platinum-based chemotherapeutic regimen for primary disease treatment. Patients were allowed to receive but were not required to receive two additional cytotoxic regimens.
No condition or anomaly that would preclude with appropriate placement of IP catheter for EGEN-001 administration
No active autoimmune disease
No prior radiation therapy to abdomen nor pelvis

Trial Design was a standard 3+3 phase I dose escalation with patients receiving PLD every 28 days and EGEN-001 ip on days 1,8, 15, 22 of a 28 day cycle. Cycles were repeated every 28 days until disease progression.

Dose Level	EGEN-001 (mg/m² ip) Weekly	PLD (mg/m² iv) Day 1 of Each Cycle
1	24	40
2	36	40
3	36	50

Results

- **Sixteen patients were enrolled from September 2012 until July 2014?2.**
- **No DLTs were found during cycle one of each dose level.**
- **Adverse Events:**
  - **4 grade 3 Anemia**
  - **1 grade 3 Nausea**
  - **1 grade 3 Small bowel obstruction**
  - **9 grade 3/4 Neutropenia**

Number of Courses Received – All Eligible and Treated Patients

- **There were minimal side effects of fever, flu-like symptoms, and infusion or injection-site reactions.**

Number of Courses Received- All Eligible and Treated Patients

	All n (%)	EGEN-001 24 mg/m2 IP weekly + PLD 40 mg/m2 IV Day 1 n (%)	EGEN-001 36 mg/m2 IP weekly + PLD 40 mg/m2 IV Day 1 n (%)	EGEN-001 36 mg/m2 IP weekly + PLD 50 mg/m2 IV Day 1 n (%)
Total	16	4	5	7
Number of Courses				
1	4 (25.0%)†	1 (25.0%)	2 (40.0%)	0 (0.0%)
2	5 (31.3%)†	2 (50.0%)	1 (20.0%)	1 (14.3%)
3	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
4	1 (6.3%)†	0 (0.0%)	0 (0.0%)	1 (14.3%)
6	3 (18.8%)	1 (25.0%)	1 (20.0%)	1 (14.3%)†
7	1 (6.3%)†	0 (0.0%)	0 (0.0%)	2 (28.6%)
8	1 (6.3%)	0 (0.0%)	1 (20.0%)	1 (14.3%)

•Objective Tumor Response in Measurable Disease Patients

	Dose Level			
	All n (%)	EGEN-001 24 mg/m2 IP weekly + PLD 40 mg/m2 IV Day 1 n (%)	EGEN-001 36 mg/m2 IP weekly + PLD 40 mg/m2 IV Day 1 n (%)	EGEN-001 36 mg/m2 IP weekly + PLD 50 mg/m2 IV Day 1 n (%)
Total	14	2	5	7
Objective Tumor Response				
Partial Response	3 (21.4%)	0 (0.0%)	1 (20.0%)	2 (28.6%)
Stable	5 (35.7%)	0 (0.0%)	1 (20.0%)	4 (57.1%)
Increasing Disease	3 (21.4%)	2 (100.0%)	1 (20.0%)	0 (0.0%)
Not Evaluable	3 (21.4%)	0 (0.0%)	2 (40.0%)	1 (14.3%)

Conclusions

•The highest clinical benefit of 85.7% was seen in dose level 3 of EGEN-001 36mg/m² weekly along with pegylated doxorubicin at 50mg/m².
•Two patients in this dose level had partial response while the remaining 4 had stable disease in a difficult to treat patient population.
•The translational studies from this trial are ongoing.
• EGEN-001 with pegylated liposomal doxorubicin has significant clinical benefit and warrants further development with escalating doses of EGEN-001 in the recurrent ovarian cancer patient population.

References

1. **Anwer K, Barnes MN, Fewell J, Lewis DH, Alvarez RD. Phase I clinical trial of IL-12 plasmid/lipopolymer complexes for the treatment of recurrent ovarian cancer. Gene Ther 2010;17:360-9.**
2. **Anwer K, Kelly FJ, Chu C, Fewell JG, Lewis D, Alvarez RD. Phase I trial of formulated IL-12 plasmid in combination with carboplatin and docetaxel chemotherapy in the treatment of platinum-sensitive recurrent ovarian cancer. Gynecol Oncol 2013;131:169-73.**