PROTOCOL ABSTRACT

Protocol: (Give number and abbreviated title) (Two lines not to exceed 75 characters per line Use 12 point only)

A Phase I study of Ad-p53 for patients with platinum- and paclitaxel-resistant epithelial ovarian cancer

Study Chairman: Judith K. Wolf, M.D.

Objectives: (Twelve lines not to exceed 75 characters per line)

1. To determine the maximum tolerated dose of the wild-type p53 adenovirus vector in patients with platinum-resistant ovarian cancer.
2. To determine qualitative and quantitative toxicity and reversibility of toxicity of this treatment approach.
3. To document observed anti-tumor activity of this treatment approach.
4. To evaluate biological endpoints including the ability of ad-p53 to infect tumor cells, express p53 and induce apoptosis.

Rationale: (Twelve lines not to exceed 75 characters per line)

- Ad-p53 is a replication deficient adenovirus containing human p53 cDNA. In preclinical studies in ovarian cancer has been found to inhibit the growth of ovarian cancer cells in vitro and in vivo in nude mouse studies regardless of the endogenous p53 status of the cells.
- In a phase I trial in recurrent squamous carcinoma of the head and neck it has been found to be safe to a dose of $10^{10.5}$ plaque forming units (PFU). In the present study we are testing the safety of giving Ad-p53 as an intraperitoneal therapy, beginning at a dose of 10^9 (PFU) each day for 5 days every 3 weeks. This dose schedule was chosen as multiple treatments are found to be efficacious in the nude mouse model.

Patient Eligibility: (Twenty lines not to exceed 75 characters per line)

Eligible Patients

1. Histologically confirmed metastatic epithelial ovarian cancer that is platinum and paclitaxel resistant (see section 4.1.1 for definition of platinum- and paclitaxel-resistance)
2. Patients must have received both platinum and taxol containing regimens.
3. Patients must have adequate bone marrow, liver and renal function.
4. Patients must have a life expectancy of at least 12 weeks.
5. Zubrod performance status of 0, 1 or 2.
6. Patients with lesions of any diameter or non-measurable disease but increased CA-125 $\geq$ 35.
7. All patients must be at least 30 days from completion of last chemotherapy regimen.

Ineligible Patients:

1. Patients with borderline or low malignant potential tumors.
2. Patients who are HIV positive.
3. Patients with prior malignancy less than 5 years form diagnosis, other than skin (excluding melanoma).

Treatment Plan: (Include dose adjustment) (Twenty lines not to exceed 75 characters per line)

1. The study will be an open label, upward dose ranging study for the adenovirus-p53 vector (Ad-p53).
2. Patients will undergo laparoscopy for assessment of the peritoneal cavity, obtaining ascites or peritoneal washings, tumor biopsies, and performing lysis of adhesions as indicated. At the time of laparoscopy, a Tenckhoff intra-peritoneal (I.P.) catheter will be placed.
3. Within 7 days after laparoscopy, the patients will receive daily I.P. treatment for 5 days every 3 weeks as long as there is no tumor progression. After one year, patients will be evaluated for continuation of therapy.
4. Treatment will consist of Ad-p53 given in 50 ml of Dulbecco phosphate buffered saline over 5 minutes. Up to 500ml of saline will be given after the virus has been given in the catheter..
5. All patients will be registered with the data management office.
6. Dose escalation: Eligible patients will be enrolled into one of the following Ad-p53 treatment cohorts, according to the following dose-escalation scheme:

Cohort 1:	3×10^{10} vp/mL daily for 5 days
Cohort 2:	3×10^{11} vp/mL daily for 5 days
Cohort 3:	1×10^{12} vp/mL daily for 5 days
Cohort 4:	3×10^{12} vp/mL daily for 5 days

The maximum possible dose of roughly 15×10^{12} vp/ml is dependent on estimated total virus production capacity. Patients entered on a given dose will not be eligible for dose escalation. Dose escalation may proceed after a minimum 2 week follow-up of the last patients entered into the previous dose level.

Statistical Considerations: (Twelve lines not to exceed 75 characters per line)

Three patients will be entered at each dose level with 6 patients entered at the maximum tolerated or maximum attainable dose (limitations imposed by production of the adenovirus). A maximum of 30 patients will be entered into the study.

ient Evaluation: (Twenty lines not to exceed 75 characters per line)

Pretreatment Evaluation:

- A complete history and physical to include performance status, recent weight loss, usual weight, and concurrent non-malignant disease and therapy. All prior anti-cancer treatments must be recorded.
- Screening and Pretreatment Tests:P

  Before screening begins, the patient must be informed about all aspects of the study and have signed the IRB-approved informed consent form.

  Laboratory studies shall include quantitative immunoglobulins, a CBC with differential and platelet count: SMA-12 and electrolytes including creatinine, bilirubin, SGPT, PT/PTT, & INR, alkaline phosphatase, HIV analysis, urinalysis, CA 125, CT scan of the abdomen and pelvis and chest x-ray.
- Any residual toxicity from prior therapies should be recorded by using grading schema in Appendix B.
- Appropriate studies should be obtained to fully define the extent and severity of existing or suspected malignant or non-malignant disease.
- Location, type, and size of all measurable lesions must be recorded prior to treatment. At least one lesion representative of all involved organ sites must be recorded.

Evaluation during study:

- Patients will be assessed weekly as follows:

  History, PE, performance status and weight will be performed on days 8, 15, 21 of each cycle.

  Peritoneal fluid (10 ml) or washings from the I.P. catheter will be obtained on Days 1-6, 8, & 15, of 1st 2 cycles for histologic verification, evaluation and hybridization.

  Blood will be drawn for CBC, diff, platelet count, PT and INR, PTT, total protein, albumin, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, phosphorus, calcium, SGPT, sodium, potassium, chloride, bicarbonate, CA-125 and archival serum sample (5cc) prior to each cycle.

  Blood will also be drawn for adenovirus DNA by PCR on Day 8 of each cycle.

  Serum will be tested for antibodies to adenovirus proteins prior to each cycle during treatment, every three months for the remainder of the year and at least once year thereafter.

If measurable disease is present, CT scan will be done on Day 21 of every other cycle.

Treatment will be continue upto 2 cycles after CR is achieved or 6 months for PR & then stable disease.