

Protocol Abstract

A Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Epithelial Ovarian Cancer that Overexpresses HER-2/*neu*

STUDY CHAIRMAN:

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PATIENT ELIGIBILITY:

1. Patients with advanced metastatic breast and/or ovarian carcinoma refractory to standard chemotherapy and hormone therapy.
2. Patients must have easily accessible pleural effusion and/or ascites.
3. Patients must carry tumors that overexpress HER-2/*neu* oncoprotein.
4. Patients must be willing to undergo serial aspiration of pleural/peritoneal effusion.
5. Performance status ≤ 3 .
6. Signed informed consent.

TREATMENT PLAN:

Upon confirmation of eligibility and signing a consent form, a pleural/peritoneal tap will be performed. Baseline E1A and HER-2/*neu* expression, as well as other characteristics, such as cellularity, LDH, pertinent tumor markers (CEA or CA-125 and p185), will be assessed.

In the same procedure, E1A Lipid Complex will be administered in the pleural/peritoneal cavity. The starting dose will be 1.8 mg DNA/m² complexed to the lipid carrier at a ratio of 1 mg DNA:10 mM lipid administered as a solution over 5 to 15 minutes. The patients will be asked to change positions every 15 minutes for an hour, to assure full distribution of the E1A Lipid Complex throughout the serosal cavity. Subsequent dose levels will be reached by 100 percent dose escalations (3.6, 7.2, 14.4 mg DNA/m²) in the absence of biological effects, and 25 percent dose escalations after grade ≥ 2 biological effects are observed. All dose levels will include patients with breast and ovarian cancer. Once toxicity or biologic activity (≥ 25 percent suppression of HER-2/*neu*) is detected, separate dose escalations will be done.

The pleural/peritoneal tap will be repeated at 72 hours and on days 7, 15, 22 and 28 to assess the efficiency of E1A expression in the residual malignant cells, as well as the degree of HER-2/*neu* oncoprotein suppression. The dose of E1A Lipid Complex will also be repeated weekly. A course of therapy will include three weekly doses and one week of rest.

PATIENT EVALUATION:

- Baseline history and physical examination, repeated with each course.
- CBC, with differential and platelets at baseline and weekly thereafter.
- SMA-12-100, P185, and CEA, CA15.3 (breast cancer) or CA 125 (ovarian cancer) at baseline. Repeat SMA-12-100 monthly, and tumor markers monthly if initially abnormal.
- Pleural/Peritoneal fluid measurement of LDH, p185, and CEA (breast cancer) or CA-125 (ovarian cancer) cellularity, E1A and HER-2/*neu* expression in cancer cells. These should be repeated weekly for the first month and at the time the patient is removed from study.
- Tumor cells will have S-phase fraction or PCNA evaluated at baseline, and weekly thereafter.
- A chest x-ray and CT scan of the abdomen will be performed at baseline. In case of pleural effusion, the chest x-ray will be repeated monthly. The CT scan of the abdomen will be repeated every other month, and at the time the patient goes off study.
- Other imaging studies will be performed to assess the extent of metastatic disease, and repeated every two to four months to assess response status.
- Spirometry and DLCO will be performed at baseline, and repeated one and two months later, and at the time study participation concludes.

MISCELLANEOUS INFORMATION:

STATISTICAL CONSIDERATIONS:

This will be a phase I study. Three patients will be entered at each dose level. If one patient experiences grade ≥ 3 toxicity, that level will be expanded to include six patients. The maximum tolerated dose (MTD) will be that dose at which less than two of six patients experience grade ≥ 3 toxicity. The maximal biologically active dose (MBAD) will be that dose that achieves ≥ 50 percent suppression of HER-2/*neu* expression. Once toxicity or biological activity (≥ 25 percent suppression of HER-2/*neu* is detected), separate dose escalations will be done and separate MBAD or MTD will be determined for breast and ovarian cancers.

OBJECTIVES:

1. To demonstrate E1A gene transduction into malignant cells after the administration of E1A Lipid Complex by intrapleural/intraperitoneal administration.
2. To determine whether E1A gene therapy can down-regulate HER-2/*neu* expression after intrapleural/intraperitoneal administration.