



Memorial Sloan-Kettering
Cancer Center

Update

IN GYNECOLOGIC ONCOLOGY

PROGRESS TOWARD INDIVIDUALIZED CANCER CARE

Vaccine Trials for Ovarian Cancer

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The treatment course for advanced ovarian cancer is notable for substantial chemotherapy sensitivity in patients at the outset. At relapse, subsequent and repeated chemotherapy responses often result in second or third remission until broad chemotherapy resistance develops [1]. Patient outcome could be improved by applying effective “consolidation” approaches to those in a complete primary or subsequent remission [2].

Immunotherapy approaches are well suited for evaluation in the remission setting. Ongoing trials generally focus on the effector phase of the response and seek to 1) produce an antibody response; 2) provide for the activation and/or generation of antigen-specific CD8+ and CD4+ T cells; or 3) elicit an integrated response with humoral, cellular, and cytokine effectors all directed at the target antigen. We currently have a new series of vaccine trials available to patients with ovarian cancer in complete or near complete remission (Table 1); in these trials, antibody response is the primary effector.

Ovarian cancers express multiple cell-surface antigens. A series of studies at MSKCC have defined the best strategy to produce antibodies against single cell-surface antigens; this strategy entails chemically conjugating the antigen to a highly immunogenic carrier protein (KLH), as well as making use of a saponin immunological adjuvant (QS-21 or OPT-821). Preclinical data support the hypothesis that polyvalent vaccines will likely be required [3]. We recently performed a pilot trial of a heptavalent vaccine-KLH conjugate plus QS-21 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer [4]. The vaccine was well tolerated. Eight of 9 patients developed antibody responses against at least 3 antigens. Fluorescence-activated cell sorting (FACS)

and complement mediated cytotoxicity (CDC) analysis showed increased reactivity against MCF7 cells in 7 of 9 patients, with some increase seen in all patients [4]. This strategy is currently being evaluated in a US-wide trial conducted by the Gynecology Oncology Group (GOG 255), randomizing patients in a second or third complete clinical remission to either the multi-valent antigen-KLH-OPT-821 construct or to OPT-821 alone. The primary endpoint is to extend the progression-free survival (PFS) at 12 months from 35% to 50% in this patient group.

Recent data suggested a benefit by the prolongation of PFS for patients receiving extended bevacizumab following primary chemotherapy as a consolidation strategy [5]. Other recent data suggested the ability of vascular endothelial growth factor (VEGF)-targeted strategies to have immunomodulatory properties [6]. Since many patients may receive VEGF-targeted agents following primary chemotherapy in the future, and the potential for immune enhancement exists, we are also conducting a pilot study of the aforementioned multivalent vaccine in GOG 255, in combination with bevacizumab. This protocol allows for a near complete remission, so that patients with asymptomatic small volume disease who are appropriate candidates to receive bevacizumab may enroll with concomitant vaccination. The primary endpoints are immunologic; increasing the time to disease progression is a secondary endpoint.

The preparation of the multivalent vaccine described above, which involves the manufacture and conjugation of multiple independent components, is challenging from both a technical and intellectual standpoint. A unimolecular pentavalent vaccine, bearing the antigens Globo-H, sTn, Tn, Lewis and TF, conjugated to KLH and QS-21, was recently

synthesized and studied in a preclinical setting [7]. Mice were immunized, and immunologic responses were seen, with the exception of the Lewis antigen. Based on the reported enzyme-linked immunosorbent assay (ELISA) and FACS data, the researchers concluded that the immunological properties of the antigens were preserved. This unimolecular multivalent platform may be loaded with a variety of antigens in the future, and the potential for therapeutic use is broad. A phase I trial is currently enrolling patients in first remission with high-risk features (suboptimal debulking, mucinous or clear cell histologic features, or failure to normalize CA-125 at third cycle). ■

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Table 1. Vaccine trials for ovarian cancer in complete or near complete remission.

Vaccine	IRB #	Target Population
Multivalent Randomized Phase II	MSK IRB 09-018 (GOG 255)	Second or third complete remission
Multivalent with Bevacizumab Pilot Study	MSK IRB 10-099	Second or third complete or near complete remission
Multivalent Unimolecular Construct	MSK IRB 09-184	First remission with high-risk features

IRB, Institutional Review Board; GOG, Gynecologic Oncology Group