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# New Type of Experimental Drug Active in Platinum-resistant Ovarian Cancers

- Women with highest expression of drug's target protein benefited most.
- If further confirmed, drug may represent new treatment option in ovarian cancer.
- Future study will compare the drug to standard chemotherapy.

WASHINGTON, D.C. — The antibody-drug conjugate DMUC5754A, a novel member of a relatively new class of drugs, showed activity in women with ovarian cancer, even those with hard-to-treat, platinum-resistant disease, in a phase I trial presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10. Those women with the highest expression of the drug's target, MUC16, gained the most benefit from treatment, which may help researchers predict which patients will benefit from treatment.

"If the activity of this drug is confirmed in additional trials, this will represent a novel type of therapy for ovarian cancer, with effectiveness in platinum-resistant ovarian cancer, which is the hardest type of ovarian cancer to treat," said Joyce F. Liu, M.D., M.P.H., an instructor in medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, Mass. "This would represent a real step forward in finding new, effective treatments for advanced ovarian cancer."

According to Liu, ovarian cancer is the leading cause of death from gynecologic cancers in the United States. It affects more than 22,000 women per year and results in about 16,000 deaths per year. One of the biggest challenges in treating ovarian cancer is the development of platinum resistance, where the cancer cells stop responding to platinum chemotherapy, one of the most effective drugs in treating this cancer. Standard chemotherapies have limited effect against these platinum-resistant ovarian cancers, and women whose cancers have become platinum-resistant inevitably have disease progression.

"The drug we tested in this clinical trial, DMUC5754A, is from a new class of drugs called antibody-drug conjugates," Liu said. "This drug consists of an antibody and a potent toxin joined by a cleavable linker. The antibody identifies a protein, MUC16, which is highly expressed in ovarian cancers, and targets the toxin to kill the cancer cells."

Unlike other cancer treatments, the antibody-drug conjugate releases the toxin with relative selectivity to the MUC16-positive cancer cells. This allows delivery of drugs that would otherwise be too toxic for treatment, according to Liu.

She and her colleagues evaluated the safety, pharmacokinetics and pharmacodynamic activity of DMUC5754A in 44 patients with advanced, recurrent, platinum-resistant ovarian cancer. Researchers reported one complete response and four partial responses. All five of these confirmed responses occurred at the 2.4-mg/kg dose and in patients with high expression levels of MUC16 in their cancer cells.

During the study, two dose-limiting toxicities occurred: one grade 4 neutropenia and one grade 4 uric acid increase, which occurred at the maximum administered dose of 3.2 mg/kg. Grade 3 adverse events included fatigue in 9 percent of patients and neutropenia in 9 percent of patients. Fatigue was the most common adverse event at all dose levels and occurred in 57 percent of patients. Other commonly reported adverse events were nausea, vomiting, decreased appetite, diarrhea and peripheral neuropathy.

Liu and her colleagues next plan to evaluate this drug in comparison with standard chemotherapy.

DMUC5754A is being developed by Genentech, a member of the Roche Group.

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**Abstract Number:** LB-290

**Presenter:** Joyce F. Liu, M.D., M.P.H.

**Title:** Targeting MUC16 with the antibody-drug conjugate (ADC) DMUC5754A in patients with platinum-resistant ovarian cancer: a Phase I study of safety and pharmacokinetics

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**Background:** MUC16 is a large transmembrane protein overexpressed by the majority of ovarian cancers (OC), compared with normal tissues. The role of MUC16 in the pathogenesis of is unknown; however, MUC16 may facilitate the binding of ovarian tumor cells to mesothelial cells lining the peritoneal cavity, and may inhibit natural killer cell-mediated anti-tumor cytotoxic responses. Conjugation of a highly potent cytotoxic drug to a MUC16-specific monoclonal antibody represents a novel approach to treatment of MUC16-expressing tumors. DMUC5754A is an ADC containing the humanized IgG1 anti-MUC16 monoclonal antibody linked to the potent anti-mitotic agent MMAE and demonstrates anti-tumor activity in MUC16-expressing tumor xenograft models.

**Methods:** This Phase I study evaluated safety, pharmacokinetics (PK), and pharmacodynamic (PD) activity of DMUC5754A (0.3-3.2 mg/kg) given every 3 weeks (q3w) to patients with advanced recurrent platinum-resistant OC. A standard 3+3 design was used to determine the maximum-tolerated dose, followed by cohort expansion. Tumor tissue was assessed for expression of MUC16 and other relevant markers. Clinical activity was evaluated per RECIST.

**Results:** Forty-four patients (22 escalation, 22 expansion at 2.4 mg/kg), median age 62 (44-79), ECOG PS 0-1, received a median of 4 doses (range 1-20) of DMUC5754A. Two DLTs, 1 Grade 4 neutropenia and 1 Grade 4 uric acid increase, occurred at the maximally administered dose of 3.2 mg/kg. Grade $\geq$ 3 related adverse events (AE) occurring in $\geq$ 5% of patients included fatigue (4 at 2.4 mg/kg; 9% total) and neutropenia (1 at 3.2 mg/kg, 3 at 2.4 mg/kg; 9% total). The most common related AEs over all dose levels were fatigue (57%), nausea (34%), vomiting (27%), decreased appetite (25%), peripheral neuropathy (25%), and diarrhea (23%). Serious drug-related AEs (SAE) were small intestine obstruction (2 patients), hypocalcemia (1 patient), and neutropenia (1 patient). Total antibody and conjugated MMAE were not impacted by circulating CA125 and displayed dose-dependent PK with clearance decreasing as dose increased.

Accumulation of total antibody, conjugated MMAE and free MMAE was not observed due to their short half-lives (≤5 days). Tumor MUC16 expression was evaluable in 42 patients, showing 20% IHC 0, 16% IHC 2+, and 64% IHC 3+. All confirmed responses (1 CR and 4 PRs) occurred in patients treated at 2.4 mg/kg and whose tumors were MUC16 IHC 2+ or 3+. Six additional patients had minor responses (3 at 2.4 mg/kg). Sixteen of the twenty-nine patients at 2.4 mg/kg were on study ≥ 105 days. Human epididymis protein 4 was a potential surrogate marker for serologic response measures in the presence of anti-MUC16/CA125-binding therapy.

**Conclusions:** DMUC5754A at 2.4 mg/kg q3w has an encouraging safety profile and evidence of anti-tumor activity in MUC16-expressing OC. Further studies are planned.