

COX-II inhibitors in Gynecologic Malignancies

My name is Mark Einstein and I am an Assistant Professor of Gynecologic Oncology at the Albert Einstein College of Medicine in Bronx, NY. My academic department has supported my expenses to attend this meeting. I have not been asked to speak to you today by any pharmaceutical company, however one of my clinical trials is partially supported by an unrestricted grant from Pfizer

As a Gynecologic Oncologist, I am committed to finding new therapies to prevent or treat women's gynecologic cancers. I work in the Bronx where we have some of the highest reported rates of cancers of the endometrium, cervix, vulva and vagina. It is for this reason that throughout my career I have embarked on studies that examine potential new therapies for Gynecologic Cancers. Among the most exciting are the COX-II inhibitors.

Expression of COX-II has been identified in many human cancers including: colon cancer, gastric cancer, esophageal cancer, bladder cancer, head and neck cancer, liver cancer, pancreatic cancer, prostate cancer and breast cancer¹⁻¹¹. Furthermore, COX-II inhibitors inhibit tumor proliferation even in cells that do not express COX-II¹². This suggests an alternative mechanism of action not yet defined that may play a role in inhibiting the growth of cancer tissue. The enhanced expression of COX-II has led investigators to use COX-II inhibitors in the prevention and/or treatment of colon and prostate cancers both *in vivo* and *in vitro*¹³⁻¹⁹. As you know, Celebrex was approved for chemoprevention of colon cancer in familial adenomatous polyposis patients.

Similar preclinical work and evidence suggests expression of COX-II exists in gynecologic cancers and also suggests efficacy in such cancers. Endometrial cancer, for instance, is the most common gynecologic cancer in the United States. The number of deaths from endometrial cancer has risen 128% since 1987²⁰. In 2004, an estimated 40,320 women will develop endometrial cancer and an estimated 7,090 women will die from endometrial cancer (American Cancer Society Facts and Figures 2004). Preinvasive and well-differentiated endometrial cancers are hormonally driven and often cured with surgery alone. Higher-grade tumors are usually not hormonally driven and proliferate via unknown mechanisms. These tumors are largely responsible for the rising death rate. Responses to toxic treatment protocols for women with recurrent endometrial cancer are dismal. Unfortunately, these generally older women also often have co morbidities, which limit their eligibility and tolerability of chemotherapy and radiation therapy treatments.

Since COX-II expression is seen in the endometrium and in other hormonally dependent tumors, we have investigated the expression of COX-II in endometrial cancer. Our preclinical work in human tissues, which has been confirmed by others, revealed high rates of COX-II expression in the most chemo-refractory endometrial tumors^{21,22}. These data led us to begin a pilot trial using Celebrex in women with these tumors. This trial is grant-supported by the American College of Obstetricians and Gynecologists and

partially funded by an unrestricted grant from Pfizer. Due to recent events, this trial is suspended pending the results of this meeting.

Similar data is being observed in human tissues of women with ovarian cancer (numerous references). An estimated 25,580 women were diagnosed with ovarian cancer last year and 16,090 died from it. Our survival rates using toxic chemotherapy regimens have not changed in over 15 years. Many new families of targeted agents are being tested for women with ovarian cancer. COX-II inhibitors are one of the family of targeted agents that are being proposed for potential prophylaxis for women at high risk for ovarian cancer.

COX-II expression is also strongly expressed in the primary tumor and metastatic site in human cervical cancer²³. Although cervical cancer is no longer a common tumor in the United States, it is the number one cancer killer of women in many third world countries. COX-II inhibitors are one of the family of targeted agents that are being proposed for potential prophylaxis for women at high risk for cervical cancer. Currently, two of the suspended Gynecologic Oncology Group (GOG) and Southwest Oncology Group (SWOG) trials (GOG-207, SWOG-S0212) were designed to observe the effects of Celebrex in preinvasive cervical cancers.

In summary, gynecologic cancers remain a critical issue in women's health. In many instances, treatments have not been effective at limiting the death rate. Current regimens usually include toxic chemotherapy regimens and radiation therapy, which is often not tolerated by these generally elderly women with co-morbidities. The thought of using a targeted agent such as COX-II inhibitors that has significantly less toxicities than most of the common chemotherapy agents used for gynecologic cancers has many gynecologic oncologists such as myself excited. As you know, the trials that have begun and those that were planned are all on hold. I urge the committee to take into account the potential benefits of COX-II inhibitors for the prevention or the treatment of gynecologic cancers when weighing the risks and benefits of this important class of drugs.

Respectfully submitted,

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