Dana-Farber Cancer Institute

Institute Research Shines at Society of Gynecologic Oncology Annual Meeting

The breadth and promise of clinical and basic research in gynecologic cancers was omnipresent at the annual meeting of the Society of Gynecologic Oncology, held in Tampa in late March. Researchers in the Division of Gynecologic Oncology reported results from an array of clinical trials, gave an overview of trials currently underway, and presented promising findings from the lab.

Their presentations included:

- The launch of a phase 2 trial of a potential targeted therapy for ovarian granulosa cell tumors (OvGCTs) – rare, slow-growing tumors that account for 5-7% of all ovarian cancers and almost 90% of ovarian sex cord-stromal tumors, which form in tissues supporting the ovaries. Patients are treated first with surgery, then additional therapy if they have an advanced case of the disease. Relapses are generally treated with chemotherapy, which has only modest activity. The new trial, led by **Panos Konstantinopoulos, MD, PhD,** director of translational research in Gynecologic Oncology, is examining the safety and effectiveness of nirogacestat, an oral gamma-secretase inhibitor that targets the Notch signaling pathway, in females over age 18 with recurrent OvGCT.

- Additional results were presented from the SORAYA clinical trial, which led to the accelerated approval of the drug mirvetuximab by the U.S. Food

and Drug Administration in November 2022. The results of this study have changed the standard of care for patients with ovarian cancer that resists platinum-based chemotherapy and overexpresses a protein called folate receptor α (FRα). Such tumors account for more than 90% of all cases of ovarian cancer and tend to have poor outcomes, says the study's senior author, **Ursula Matulonis, MD,** chief of the Division of Gynecologic Oncology. In the study, patients with FRα-laden, platinum-resistant high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancers were treated with mirvetuximab soravtansine (MIRV), a compound that joins an FRα-binding antibody to maytansinoid DM4, an agent that enters cells and blocks their growth. Of 105 patients evaluated, 32.4% responded to the agent, and responses lasted a median of 6.9 months. The median survival was 15 months, and 37% of the patients were alive 24 months after beginning treatment. The safety of the treatment was consistent with what had been observed in previous studies: about half of patients experienced some degree of blurred vision, which was reversible with treatment.

- Research showing that the drug adavosertib was active but not well tolerated in patients with recurrent or persistent uterine serous carcinoma (USC), a less common but aggressive form of endometrial cancer that accounts for up to 40% of endometrial cancer mortality. Investigators led by **Joyce Liu, MD**, **MPH,** associate chief and director of clinical research in the Division of Gynecologic Oncology, tested adavosertib, which targets the enzyme WEE1, in a clinical trial enrolling 109 patients with recurrent or persistent USC who had previously been treated with one or more platinum-based chemotherapy agent. In 104 evaluable patients, the response rate was 26%. One patient had a complete response – a disappearance of all signs of cancer

– 26 had a partial response, and 42 had stable disease. Responses lasted a median of 4.7 months. While these results are encouraging, 97.2% of patients experienced adverse side effects related to the treatment, and 60.6% had a grade 3 (severe or medically significant) treated-related adverse effect. "Overall, our findings indicate that while WEE1 inhibition results in antitumor activity in USC and may remain a viable treatment target, the therapeutic window for adavosertib was narrow," Liu said. Other agents targeting Wee1 are also under investigation.

- A study suggesting that drugs targeting certain members of the BCL-2 family of proteins may be effective against certain rare, hard-to-treat forms of ovarian cancer. These subtypes – including carcinoscarcoma, clear cell endometrioid, mucinous, low-grade serous, and small cell ovarian cancer – are less responsive to platinum or taxane chemotherapy than high-grade serous ovarian cancer and often have poor outcomes when the disease is advanced or recurs. In experiments in cancer cell lines, researchers led by **Elizabeth Stover, MD, PhD**, found that most ovarian cancers, including rare subtypes, are dependent on BCL-XL, and some are dependent on MCL1, both of which are members of the BCL-2 protein family. The family is known as an anti-apoptotic group because its members deter cells from undergoing programmed cell death. The findings indicate that BCL-XL- or MCL1-targeting drugs may be promising approach to treating multiple forms of ovarian cancer.