TPS12148 **Poster Session**

A phase II randomized placebo-controlled study of fisetin and exercise to mitigate chemotherapy-related functional decline in postmenopausal women with early breast cancer (PROFFi).

Jingran Ji, Marla Lipsyc-Sharf, Yuliya Zektser, Kirsten K. Ness, Yara Abdou, Poorni Manohar, Heather L. McArthur, Mylin Ann Torres, George A. Kuchel, Arash Naeim, Catherine M. Crespi, Beverly Canin, Patricia Spears, Sandra Finestone, Ali Al Saleem, Joseph D. Olivera, Kelly S. Synold, Laura Petersen, Hyman Muss, Mina S. Sedrak; UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA; St. Jude Children's Research Hospital, Memphis, TN; Division of Oncology, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; UT Southwestern, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; Division of Health Services, Outcomes, and Policy, Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; University of Connecticut, Farmington, CT; University of California, Los Angeles, Los Angeles, CA; SCOREboard Advisory Group, City of Hope Cancer Center, Duarte, CA; UNC Patient Advocates for Research Council, Raleigh, NC; Research Advocacy Network/Komen AIS, Irvina, CA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Despite substantial improvements in survival, postmenopausal survivors of breast cancer remain at high risk of functional decline after cancer treatment. One potentially targetable mechanism of chemotherapy-related functional decline is cellular senescence, a state of cell cycle arrest. Senescent cells (Sncs) develop a senescence-associated secretory phenotype (SASP), where they secrete a milieu of inflammatory cytokines that drive functional decline over time. In patients with stage I-III breast cancer treated with chemotherapy, markers of Sncs and SASP sharply increase after treatment and persist over time. Emerging data suggest that senolytics and exercise can decrease Snc burden. Senolytics are novel agents that eliminate Sncs and improve physical function in non-cancer populations. Among the existing senolytics, fisetin is a natural compound that is safe and tolerable in humans. Exercise also reduces Sncs in individuals without cancer and is well-established to improve physical function in survivors of cancer. More recent pre-clinical data shows that senolytics combined with exercise led to a greater reduction in Sncs than either intervention alone. However, no studies have tested whether senolytics and exercise, either alone or in combination, can reduce Sncs and improve physical function in cancer survivors. Therefore, we hypothesize that targeting Sncs with a combination of fisetin and exercise will lead to both independent and synergistic effects to prevent physical function decline in postmenopausal breast cancer survivors. **Methods:** This multicenter phase II randomized, placebo-controlled study will enroll 200 postmenopausal women with stage I-III breast cancer. Key eligibility criteria include completing neo/adjuvant chemotherapy within 12 months with diminished physical function as measured by the 6-minute walk distance (6MWD). Using a 2x2 factorial design, participants will be randomized 1:1:1:1 to exercise with fisetin, exercise alone, fisetin alone, or a control group for a total 16-week course. Fisetin will be dosed at 20mg/kg on days 1-3 every 14 days. Those randomized to the exercise arms will undergo a tailored, supervised remote exercise program led by a qualified exercise physiologist. The primary objective is to determine the effect of fisetin and/or exercise on physical function, as measured by the change in 6MWD from baseline to end of treatment. Secondary objectives include evaluating the effect of exercise and/or fisetin on other measures of physical, cognitive, psychosocial, and cardiometabolic function as well as digital biomarkers. We will also examine the effect of exercise and/or fisetin on markers of Sncs and SASP. Enrollment on this study began July 2024 and is currently ongoing (NCT06113016). Clinical trial information: NCT06113016. Research Sponsor: U.S. National Institutes of Health; R01 CA280088.