Characterization of residual disease after neoadjuvant selective estrogen receptor degrader (SERD) therapy using tumor organoids in the I-SPY2 Endocrine Optimization Protocol (EOP)

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BACKGROUND
- Treatment of estrogen receptor (ER)-positive breast cancer with selective estrogen receptor degrader (SERDs) frequency results in the loss or reduction of ER expression. Whether these changes are due to on-target effects of SERDs disrupting ER or as a mechanism of tumor resistance with associated changes in cellular phenotypes is unknown.
- It is critical to distinguish between these possibilities to assess treatment response and determine the most appropriate subsequent therapy.
- We created and conducted molecular analyses on patient-derived organoid cultures from post-treatment tissue in patients receiving neoadjuvant SERD therapy for early-stage ER+ breast cancer in the I-SPY2 Endocrine Optimization Protocol (EOP).

THE EOP STUDY
- In the change in ER expression reflective of drug effect or of a shift in tumor subtype (e.g., from luminal to basal) that would warrant a change in adjuvant therapy.

RESULTS
- Decreased ER expression in residual disease

Figure 3: Decreased ER expression in residual disease

Figure 4: Generation of organoids from residual disease

Figure 5: Immunohistochemistry results per case, pre-versus post-treatment, and tumor change on MRI

Figure 6: Examples of organoids displaying solid or epithelial morphologies (from post-treatment samples)

Figure 7: Patient-derived EOP organoid cultures

Figure 8: Examples of ER protein expression in organoids.

Table 1: Number of patients on study who have gone to surgery by category

Figure 9: Single-cell RNA-seq sequencing results of early passage organoid cultures from EOP post-treatment tissue.

Figure 10: GATA3 expression in post-treatment tumors.

SUMMARY & FUTURE DIRECTIONS
- Our anticipated results in different scenarios: samples showing "no target effect" (ER expression turned back on in organoids cultured with a SERD), breast cancer subtype changed post-treatment, other markers unchanged, (e.g., GATA3, ER, PR).

Table 2: Features of organoids cultured with a SERD.

Advocate statement
- "ER expression suppression in organoids created with post-surgical residual tissue treated preclinically with a SERD may be a useful tool in determining whether to use endocrine or other post-surgical therapies. This preliminary promising result, which will be further explored, should be continued to more precisely target endocrine treatment and be evaluated in the I-SPY2 EOP trial.

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References