# PS1-13-20 Functional Precision Oncology for Metastatic Breast Cancer (FORESEE): A Feasibility Trial. Final Results.

Christos Vaklavas[1], Ling Zhao[1], Chieh-Hsiang Yang[1], Sandra D. Scherer[1], Xiaomeng Huang[1], Saundra S. Buys[1], Mei Wei[1], Philip Moos[1], Gabor Marth[1], Bryan E. Welm[1], Alana L. Welm[1]

[1]Huntsman Cancer Institute, University of Utah

## Background

Next Generation Sequencing (NGS) has allowed for the identification of cancer driver mutations and the development of drugs that directly target the resulting mutated proteins.

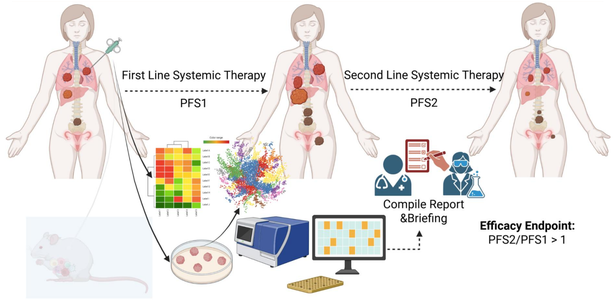
Many cancers do not harbor targetable or actionable driver mutations identified by NGS, and even if an actionable mutation is identified, it is unknown whether inhibition of that target will lead to clinical response[1].

Molecular profiling alone insufficiently captures the biologic complexities, most notably heterogeneity and plasticity, of metastatic cancer and informs only the selection of a targeted therapy. Conventional chemotherapy still constitutes the most effective treatment option for many metastatic cancers, especially triple negative breast cancer.

Patient Derived Organoids (PDOs) retain faithfully the phenotypic and genomic features of the originating tumors and are amenable for medium throughput drug profiling studies[2,4]. PDOs may allow for more reliable and accurate predictions about the activity of a drug in the clinic.

FORESEE is the first prospective clinical trial where patient derived models were generated and functional drug screens were performed to inform medical decisions in metastatic breast cancer.

## Workflow




Tumor tissue was acquired from eligible patients for PDO establishment and single cell sequencing. Circulating tumor (ct) DNA was also collected. Unlike our previous study (TOWARDS 1)[3], xenografts in mice were not generated. After the biopsy was performed, patients began therapy at the discretion of the treating physician. The results from ct and tumor tissue DNA sequencing were compiled along with the results from PDO drug screening in a single report that was shared and discussed with the treating physician.

## Study Schema

**PART 1** **PART 2**

**Key Inclusion Criteria**

1. Metastatic or recurrent unresectable breast cancer.
2. Her2 negative on IHC or nonamplified by FISH.
3. Triple negative breast cancer (TNBC): no prior treatment in the metastatic setting
4. Hormone receptor (+) & Her2 (-) (HR +/Her2): exhaustion of endocrine options.
5. Tumor content ≥20% on biopsy
6. Measurable or evaluable disease.

**Key Exclusion Criteria**

1. Uncontrolled significant intercurrent illness
2. ECOG PS >2.
3. Inability to acquire tumor tissue.

**Enroll 3 patients** → **Evaluate workflow & process** → **TNBC 6 patients** / **HR+/Her2- 6 patients**

**Primary Objective**
Assess the feasibility of genomic characterization & drug screening in a clinically relevant timeframe.

**Primary Endpoint**
Proportion of cases where clinically actionable outcomes were identified by functional precision oncology by 12 weeks.

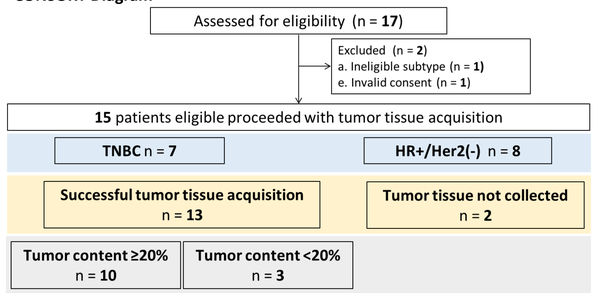
**Secondary Objectives**

1. Assess the time required to return genomic characterization & drug screening results to treating physicians.
2. Assess the performance & concordance of our integrated functional genomic assays against commercially available assays.

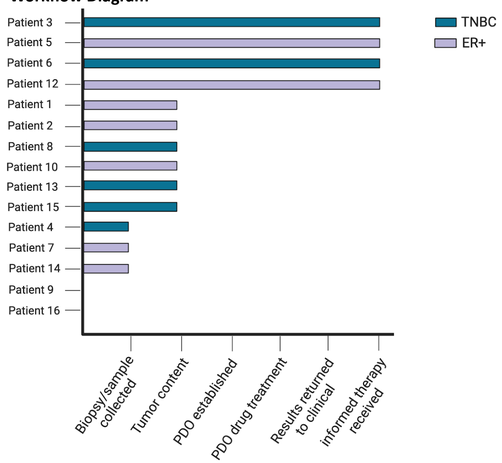
**Exploratory Objective**
Assess the clinical efficacy of treatment decisions informed by functional genomic assays compared with decisions not informed by functional genomic assays.

## Results

**CONSORT Diagram**



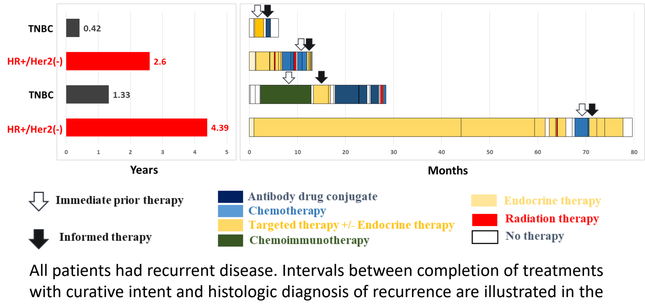

**Workflow Diagram**




PDOs were successfully established and vigorously validated in 4/10 (40%) of patients with adequate tumor content (≥20%). PDOs could not be established from tumor tissue acquired from liver metastases. Patients with liver-only metastases were excluded from Part 2. Once established, drug profiling was successfully performed and the results were returned within 12 weeks.

## Results

**Characteristics & Natural History of Patients with Successful PDO Drug Screen**




All patients had recurrent disease. Intervals between completion of treatments with curative intent and histologic diagnosis of recurrence are illustrated in the left panel. Patients with HR+/Her2- breast cancer relapsed while on adjuvant endocrine therapy. In all cases, PDO drug profiling informed treatment selection. In 3/4 cases, the informed therapy constituted the last or near-last therapy that the patient received.

A. In 3/4 cases, genomic studies did not reveal mutations to match FDA approved therapies.
B. In 1/4 cases, commercial genomic studies identified an actionable mutation (*PIK3CA*, p.H1047R). Research genomics identified additional aberrations along the PI3K-AKT1-mTOR pathway, downstream of the PI3K, suggesting that a PI3K inhibitor would have not been effective. In line with these findings, PDO drug screening was consistent with an unusually strong response to everolimus (which the patient received) while alpelisib was ineffective in clinically relevant concentrations.
C. In all cases, PFS achieved with the informed therapy (PFS2) did not exceed the PFS achieved with the immediate prior therapy (PFS1). PFS2:PFS1 ratios ranged between 0.26 – 0.6.

## Discussion & Conclusions

The study did not meet the primary endpoint of feasibility, defined as identification of clinically meaningful therapeutic vulnerabilities to medications available to the patient (FDA approved or investigational agents being evaluated in separate active clinical trials within the institution) by functional precision oncology by 12 weeks in >46% of cases. Our success rate was 40%.

Failure to establish stable PDOs constituted the primary reason of infeasibility, while performing drug profiling studies late in the natural history of metastatic breast cancer may have also limited the potential efficacy of the PDO-informed therapies.

## Contact

Christos Vaklavas
Huntsman Cancer Institute
Email: christos.vaklavas@hci.utah.edu
Website: https://uofuhealth.utah.edu/huntsman/labs/welm-labs
Phone: 801 213 8477

## References

1. Andre F, *et al.* **Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER).** Lancet Oncol. 2014 Mar;15(3):267-74.
2. Guillen KP, *et al.* **A human breast cancer-derived xenograft and organoid platform for drug discovery and precision oncology.** Nat Cancer 2022 Feb;3(2):232-250.
3. Vaklavas C, *et al.* **TOWARDS Study: Patient-Derived Xenograft Engraftment Predicts Poor Survival in Patients With Newly Diagnosed Triple-Negative Breast Cancer.** JCO Prec Oncol. 2024 Jul:8:e2300724.
4. Scherer SD, *et al.* **Breast cancer PDxO cultures for drug discovery and functional precision oncology.** STAR Protoc 2023 Sep 15;4(3):102402.
5. Images created at **BioRender.com**

This presentation is the intellectual property of the author/presenter. Contact them at christos.vaklavas@hci.utah.edu for permission to reprint and/or distribute.

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com