PRETREATMENT SERUM METABOLOME PREDICTS PFS IN FIRST-LINE TRASTUZUMAB-TREATED METASTATIC BREAST CANCER.


1Olaris, Inc., Cambridge, MA, 2Penn State Hershey Medical Center, Hershey, PA, 3Penn State Hershey Medical Center, Lebanon VA Medical Center, Hershey, Lebanon, PA, 4Arizona Metabolomics Laboratory, College of Health Solutions, Arizona State University, Scottsdale, AZ, 5Pinnacle Health System, Harrisburg, PA, 6Walt Carney Biomarkers Consulting, LLC, North Andover, MA, 7Medical University of Vienna, Vienna, Austria.

WHAT IS THE PROBLEM?

HER2-positive (HER2+) metastatic breast cancer (mBC) patients have significant heterogeneity in response and progression-free survival (PFS) to HER2-targeted therapy trastuzumab. Several resistance mechanisms have been identified including impaired signal binding to HER2 through receptor variants or molecular masking, constitutive activation of signaling pathways parallel or downstream of HER2 such as CDK4/6, PI3K/AKT, and mTOR pathways, or reduced immune system activation such as escape from antibody-dependent cellular cytotoxicity (ADCC). Overexpression of Fatty Acid Synthase gene (FASN) has also been associated with poor clinical response to anti-HER2 therapy. Few if any biomarkers have been clinically validated to identify patients who will have a durable response to anti-HER2 therapy.

OBJECTIVE(S)

1. To evaluate pretreatment serum metabolomic biomarkers for correlation with PFS in a cohort of metastatic breast cancer patients from a single institution.

2. To identify potential metabolic pathways that are altered in patients with limited response to trastuzumab.

WHY METABOLITES?

Cancer cells have altered metabolism, which contributes to their ability to proliferate, survive in unusual microenvironments, and evade other tissues. Measuring the complete set of metabolites in an individual (i.e. the metabolome) provides a functional readout for cellular pathways. Further, changes in the metabolome can be correlated with disease status, prognosis, and drug sensitivity. Using a metabolomic platform and machine learning algorithms, biomarker signatures can be identified to predict response to therapy. Metabolite analysis of pretreatment serum has shown promise for predicting response in a prospective study of the CDK4/6 inhibitors palbociclib and ribociclib in hormone receptor-positive metastatic breast cancer (Zhang et al., ASCO 2019 Poster 30434). Due to the promise of this HER2+ signal in metabolomics, we hypothesized that a metabolite signature exists to correlate with trastuzumab response.

METHODS:

Pretreatment serum from 36 HER2+ trastuzumab-naïve metastatic breast cancer patients who were treated with trastuzumab were included in this exploratory analysis. Metabolites were extracted from previously frozen serum (31 mL) using a modified method. The resulting metabolites were isolated and quantified using an untargeted, non-destructive, nuclear magnetic resonance (NMR)-based profiling platform (Olaris, Inc., Cambridge, MA). The serum was analyzed via 1D and 2D NMR spectroscopy and correlation analysis. A custom trained machine learning algorithm was used to identify patients with shorter and longer PFS to trastuzumab-based therapy.

RESULTS:

The patient meta data for the 34 HER2+ mBC patients treated with trastuzumab provided in the Table below. PFS was calculated as the time from the start of trastuzumab treatment until the time of cancer progression or death. Response (R) was classified as non-response (NR) if trastuzumab was determined as a PFS score of ≤1% of median PFS of 141 days. Line describes whether patients received trastuzumab as 1st, 2nd, 3rd, or 4th line therapy. Treatment details the treatment regimen for each line where 1= single agent trastuzumab, 2= vinorelbine, 3= trastuzumab-iplomab, 4= trastuzumab-tedavalisib, 5= docetaxel, 6= trastuzumab-gevantamib. 

We performed a total of 9 analyses for this study. In Analysis A we compared all NR (N=11) vs R (N=16) in the 33 patient samples passing QC. There was minimal discrimination between R vs. NR. Previous reports have suggested that trastuzumab collection methods strongly influence metabolite levels. For this reason, we removed all samples that were collected “After” (N=7) trastuzumab infusion. For Analysis B we compared NR (N=14) vs R (N=12) for the remaining 28 patients. The ability to differentiate R vs NR was still limited. We re-examined the patient meta data and observed significant heterogeneity in the treated regimen and treatment time. For example, a few patients received trastuzumab as a mono-therapy, while the remaining received trastuzumab with chemotherapy. Further, several patients received trastuzumab as part of 1st line therapy, while others received it as 2nd, 3rd, or 4th line. For Analysis C, we compared NR (N=12) vs R (N=10) for the 22 patients who received trastuzumab as part of combination therapy. We then focused on a subset of these patients in Analysis D (N=9), who were treated with trastuzumab + chemotherapy in 1st line treatment. The results of Analysis C and D provided promising results. We also performed 2 independent analyses comparing 1) the patients with the extreme outcomes, Rapid Progressors (R) vs Slow Progressors (NR) in Analysis E and 2) comparing patients with Long (N=4) vs Liver (N=2) metastasis in Analysis F.

CONCLUSIONS & NEXT STEPS:

Using proprietary machine learning we were able to construct a model based on 5 metabolite signatures that could differentiate NR vs R in mBC patients receiving trastuzumab + chemotherapy. Further efforts are underway to confirm the identity of these metabolites. Expanded metabolomic analysis is warranted in larger cohorts and clinical trials to confirm that this serum biomarker signature predicts PFS in trastuzumab therapy, particularly in the first-line setting. Further, by identifying the metabolites and metabolic pathways that differ between early and late responders, it may be possible to identify novel targets and/or suggest combination approaches that may improve outcomes in the HER2+ metastatic breast cancer setting. In fact when we compared the patients with the extreme outcomes. Rapid Progressors (R) vs Slow Progressors (NR) we found that patients with PFS greater than 700 days, we identified 10 metabolite signatures that differed between NR vs RP, with a p-value of <0.01. Both of these panels passed the false discovery rate (FDR) and only 16 were expected by chance. This could suggest there is a significant metabolic difference between patients who have the best and worst response to trastuzumab. Additional samples will be required to verify these results.

Olaris’ BoR Can Transform Breast Cancer Treatment

Olaris is founded on the belief that collaborative research will lead to breakthrough science with the potential to change the treatment paradigm of breast cancer. Our mission is to create a future where being diagnosed includes a BoR to empower optimal treatment decisions. Let’s collaborate to make this reality a reality.

For more information, please contact

ccow@olarisbo.com

www.olarisbo.com