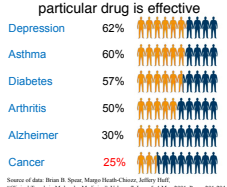
NMR-metabolite-resonance signature predicts HR+ breast cancer patient response to CDK4/6 inhibitors

Bo Zhang,[1] Chen Dong,[1] Jason Warner,[1] Christopher Pinto,[2] Dejan Juric,[2,3] Elizabeth ODay[1]

[1]Olaris, Inc., Cambridge, MA; [2]Massachusetts General Hospital Cancer Center, Boston, MA; [3]Harvard Medical School, Boston, MA. For correspondence email: eoday@olarisBoR.com

RELIABLE DATA FOR CLINICIANS TO DETERMINE THE RIGHT THERAPY FOR THE RIGHT PATIENT AT THE RIGHT TIME

Percentage of the Patient population for which a particular drug is effective



Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine", Volume 7, Issue 5, 1 May 2001, Pages 201-204

OLARIS MISSION

To fundamentally change how diseases are diagnosed and treated.

With our pioneering metabolomics platform and machine learning algorithms we produce

"Biomarkers of Response" (BoR)

to readily differentiate drug responders (R) from non-responders (NR).

A Case Study: Uncovering A CDK4/6 BoR For Metastatic Breast Cancer

Prognosis

- 155,000 women in the US live with metastatic breast cancer (mBC)
- mBC is the second leading cause of death in women in the US, taking > 40,000 lives per year
- Less than 22% of mBC patients survive +5 years

Cost of treatment

- mBC patients receive a CDK4/6 inhibitor costing $168,000 per year

Response Rates

- 20% of mBC are intrinsic non-responders (NR) to CDK4/6 inhibitors
- All patients acquire resistance to CDK4/6 inhibitors

Structure	Drug	CDK IC50	Adverse Effects	Yearly Cost
	Ibrance (palbociclib)	CDK1: >10μM CDK2: >10μM CDK4: 9-11nM CDK6: 15nM	Neutropenia, infections	$168,000
	Kisqali (ribociclib)	CDK1: >100μM CDK2: >50μM CDK4: 10nM CDK6: 39nM	Torsades, hepatotoxicity, neutropenia	$168,000
	Verzenio (abemaciclib)	CDK1: >1μM CDK2: >500nM CDK4: 2nM CDK6: 5nM	Diarrhea, VTE, hepatotoxicity, neutropenia	$168,000

Today

ER+ metastatic BC patients are prescribed CDK4/6 inhibitors

20% of patients are **intrinsically resistant**

All patients acquire resistance

- **Poor outcomes**
- **Increased adverse effects**
- **Increased healthcare costs**

The Olaris Future

Each patient is screened prior to treatment

"resistant" patients receive alternative treatment — BoR — PREDICT BEFORE TREATMENT

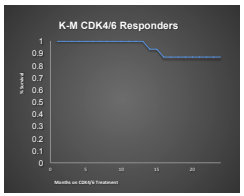
"responders" receive CDK4/6 inhibitor

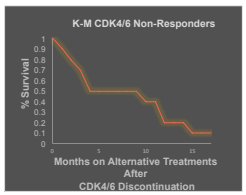
"resistant" patients receive alternative treatment — BoR — MONITOR ON TREATMENT

"responders" receive CDK4/6 inhibitor

- **Improved outcomes**
- **Reduced adverse effects**
- **Reduced healthcare costs**

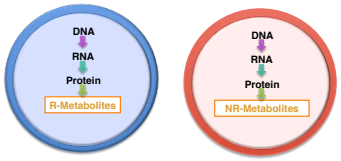
We performed a retrospective study analyzing plasma-based metabolites from a baseline (pre-dose) and ~2 months post treatment of 24 women with estrogen-receptor-positive (ER+) metastatic breast cancer treated with CDK4/6 inhibitors, Palbociclib or Ribociclib.





- **87% of Responders** [patients who saw tumors decrease within first 6 months of treatment] are **alive** + 2 years
- **90% of Non-Responders** [patients who saw tumors increase within first 6 months of treatment] are **deceased** within 12-15 months

METABOLOMICS PROVIDES QUANTITATIVE PHENOTYPING



Biomarkers

DNA/RNA: what **could** happen

Protein: what **makes it** happen

Metabolites: what ***is*** happening

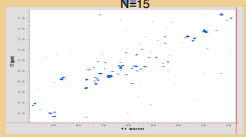
- Factors beyond genomics influence drug response (environment, nutrition, microbiome, drugs, diseases, etc.).
- By looking downstream of the genome metabolites provide the most accurate representation of phenotype
- The Olaris NMR-based-metabolomics platform can distinguish drug responder vs drug non-responder

OLARIS TECHNOLOGY PROVIDES A MEATBOLITE FINGERPRINT FOR CDK4/6 R VS NR PATIENTS

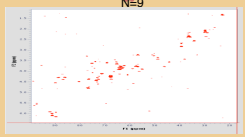
Study design: Jane vs Jill (R vs NR)

Jane on AI + CDK 4/6 inhibitor
Jane's tumor shrinks (R)
N=15

Jill on AI + CDK 4/6 inhibitor
Jill's tumor **did not** shrink (NR)
N=9

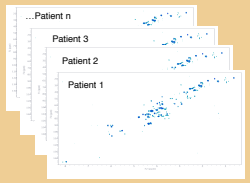


Metabolic Profile of a Responder

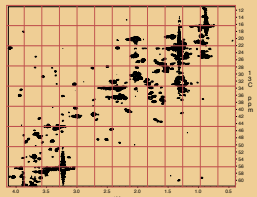


Metabolic Profile of a Non-Responder

Data Format

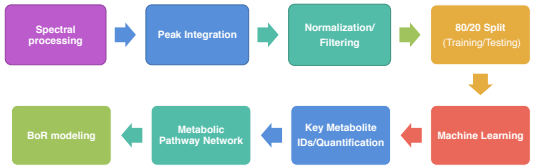


Capturing multiple NMR spectra in batch mode

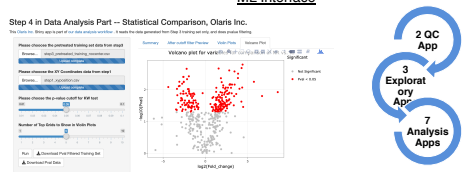


Semi-quantification of thousands of features

Workflow Chart

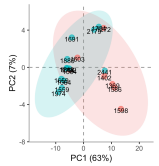


ML Interface

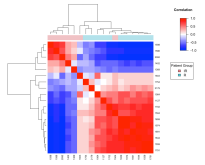


METABOLOMICS + MACHINE LEARNING IDENTIFIES SIGNATURES PREDICTIVE OF DRUG RESPONSE

Examples of Unsupervised Analysis

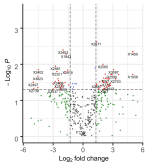


PCA scores plot

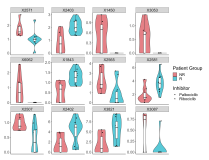


Hierarchical clustering of samples and variables

Examples of Statistical Analysis

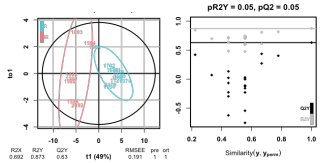


volcano plot



Violin plot

Examples of Machine Learning Analysis



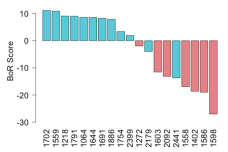
OPLS-DA (Scores Plot)

	NR	R	Error (%)
NR	99	41	29.3
R	14	196	6.7

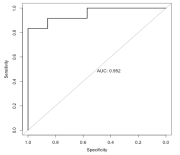
The "out-of-box" (OOB) estimate of error rate is 3.9%.

Random Forest

Olaris BoR ML model



BoR prediction model



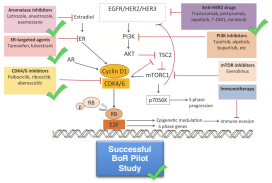
ROC Analysis

By correlating the metabolite expression profiles to clinical outcomes we were able to identify a metabolic signature that could differentiate the CDK4/6 R vs NR patients with a predictive accuracy of > 90%. Furthermore, we were able to identify independent signatures predictive of response for individual CDK4/6 inhibitors palbociclib and ribociclib.

CONCLUSION & FUTURE DIRECTIONS

The results of this study, suggest the **Olaris BoR assay can differentiate metastatic breast cancer patients that will and will not benefit from a CDK4/6 inhibitor** during the first 6 months of treatment. This could lead to a paradigm shift in the administration of CDK4/6 inhibitors wherein prior to treatment patient plasma is screened to determine whether that individual patient is responsive or resistant to a CDK4/6 inhibitor. While exciting, appropriate caution should be taken due to the sample size (N=24). Olaris is now repeating this study in larger patient cohorts to validate the clinical utility.

Breast Cancer Drugs



COLLABORATE WITH OLARIS:

We are fortunate to live in era where we have access to phenomenal therapies. However, it remains difficult to determine which therapy will benefit a particular patient. **Biomarkers of Response (BoR) can solve this problem.**

Olaris aims to develop BoRs for all breast cancer drugs. Through collaborations Olaris has already identified BoRs for CDK4/6 inhibitors, tamoxifen, aromatase inhibitors and Herceptin. We want to partner with you to expand our BoR technology. **Together we can get the right drug to the right patient.**

OLARIS