Leveraging Real World Evidence for Precision Medicine Applications and Multi-Omic Biomarker Analysis for CDx Development

Dr. Emanuel Petricoin
George Mason University
Center for Applied Proteomics and Molecular Medicine
Manassas, VA
703-993-864- phone
703-993-4288- fax
epetrico@gmu.edu
I have the following financial relationships to disclose:

• Consultant for:
  - ADVX, Inc.
  - Ceres Nanosciences, Inc.
  - Targeted Pharmaceuticals, Inc.
  - Perthera, Inc.
  - AZGen, Inc.

• Stockholder in:
  - Avant Diagnostics, Inc. (Chair SAB)
  - Perthera Inc. (Founder, Equity Stock, Chair SAB)
  - Ceres Nanosciences, Inc. (Founder, Equity Stock, BOD)
  - Targeted Pharmaceuticals, Inc (Founder, Equity Stock).

• Employee of: George Mason University

• Royalties: US Government Assigned and GMU Assigned patents on RPPA technology and nanoparticle technology
Reverse Phase Protein Arrays:
Invented at NIH in 1999
Originating article:

Reverse phase protein microarrays which capture disease progression show activation of pro-survival pathways at the cancer invasion front

Cloud P Paweletz, Lu Charboneau, Verena E Bichsel, Nicole L Simone, Tina Chen, John W Gillespie, Michael R Emmert-Buck, Mark J Roth, Emanuel F Petricoin III, and Lance A Liotta
A roadmap for individualized cancer therapy

1. Tumor biopsy
2. Microdissection
3. Protein microarray
   - HER2
   - ERBB1
   - ERBB2
   - STAT
   - ERK
   - AKT
   - MYC
   - P70S6K
   - ELK
4. Choose panel of combination therapy best suited to the molecular network defect
5. Monitor success of the therapy by conducting molecular analysis after treatment
6. If the therapy fails, repeat the process and choose a new therapy combination tailored to the recurrent tumor
Summary of RPPA Methodology

Microdissected cellular sample

384 well plate preparation

Cell lysis

Array printing

Image Analysis
MicroVigene

Immunostaining
Dako Autostainer

Protein Microarray

Sypro Ruby
total protein stain
Study Schema

I-SPY 2 was one of the first, and is now the longest-running 'platform' trial ever. As a platform trial, I-SPY 2 uses a master protocol that provides a regulatory framework to study multiple treatments in the same study. It also allows new agents to enter and leave the study without having to halt enrolment or resubmit the entire clinical trial protocol for regulatory review.

*Patients who are HER2+ may also receive trastuzumab (Herceptin)*

†An investigational combination of one or more agents may be used to replace all or some of the standard therapy
<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>HER2+HR+</th>
<th>HER2+HR-</th>
<th>HER2-HR+</th>
<th>HER2-HR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib</td>
<td>Pan ErbB Inhibitor</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ABT-888 (+ carboplatin)</td>
<td>PARP Inhibitor + carboplatin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 386</td>
<td>Angiogenesis, TIE2 Inhibitor</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 479 (+ metformin)</td>
<td>IGFR Inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MK-2206</td>
<td>AKT Inhibitor</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>ErbB2/EGFR/ ErbB3 dimerization inhibitor</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T-DM1 + Pertuzumab</td>
<td>Mertansine with above</td>
<td>Yes**</td>
<td>Yes**</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ganetespiib</td>
<td>HSP-90 Inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>

*Neratinib was delivered in place of trastuzumab in HER2+ patients.

**T-DM1 + Pertuzumab is delivered in place of paclitaxel and trastuzumab in HER2+ patients.
## Investigational Agents

<table>
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<th>Target</th>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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</table>

*Neratinib was delivered in place of trastuzumab in HER2+ patients.*

**T-DM1 + Pertuzumab is delivered in place of paclitaxel and trastuzumab in HER2+ patients.*
Evaluation of HER family protein signaling network as a predictive biomarker for pCR for breast cancer patients treated with neratinib in the I-SPY 2 TRIAL

JD Wulfkuhle1, C Yau2, DM Wolf2, RI Gallagher1, A Sanil3, L Brown-Swigart2, S Flynn2, G Hirst2, ISPY-2 TRIAL Investigators4, M Buxton2, A DeMichele5, N Hylton2, F Symmans6, L van’t Veer2, D Yee7, M Paoloni4, L Esserman2, D Berry3, M Liu8, JW Park2, EF Petricoin III1

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR Rate (95% probability interval)</th>
<th>Probability Neratinib is Superior to Control</th>
<th>Predictive Probability of Success in Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Neratinib</strong></td>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>36% (29-43%)</td>
<td>30% (23-38%)</td>
<td>72%</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>55% (46-64%)</td>
<td>32% (22-43%)</td>
<td>94%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>14% (8-19%)</td>
<td>16% (10-21%)</td>
<td>39%</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>31% (24-37%)</td>
<td>17% (10-24%)</td>
<td>91%</td>
</tr>
</tbody>
</table>
From: Katharina Feldinger, Anthony Kong.
August 20, 2015: Profile of neratinib and its potential in the treatment of breast cancer
Neratinib Drug Target Levels are Associated with pCR in Treated TN patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Control P-value</th>
<th>Neratinib P-value</th>
<th>Higher or Lower in pCR YES Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR Y1173</td>
<td>0.2441</td>
<td><strong>0.0087</strong></td>
<td>↑</td>
</tr>
<tr>
<td>ERBB2 Y1248</td>
<td>0.2441</td>
<td><strong>0.0292</strong></td>
<td>↑</td>
</tr>
</tbody>
</table>
Evaluation of the HER/PI3K/AKT Family Signaling Network as a Predictive Biomarker of Pathologic Complete Response for Patients With Breast Cancer Treated With Neratinib in the I-SPY 2 TRIAL

Julia D. Walikahle
Christina Yau
Denise M. Wolf
Daniel J. Vis
Rosa I. Gallagher
Lamorna Brown-Swigart
Gillian Hirst
Emile E. Voest
Angela DeMichieli
Nola Hylton
Fraser Symmans
Douglas Yee
Laura Esserman
Donald Berry
Minette Liu
John W. Park
Lodewyk F.A. Wessels
Laura van’t Veer
Emanuel K. Petricoin III

Purpose In the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2), the pan-erythroblastic oncogene B inhibitor neratinib was available to all hormone receptor (HR)/human epidermal growth factor receptor 2 (HER2) subtypes and graduated in the HR-negative/HER2-positive signature. We hypothesized that neratinib response may be predicted by baseline HER2 epidermal growth factor receptor (EGFR) signaling activation/phosphorylation levels independent of total levels of HER2 or EGFR proteins.

Materials and Methods Complete experimental and response data were available for between 130 and 193 patients. In qualifying analyses, which used logistic regression and treatment interaction analysis, 18 protein/phosphoprotein, 10 mRNA, and 12 DNA biomarkers that related to HER2 family signaling were evaluated. Exploratory analyses used Wilcoxon rank sum and t tests without multiple comparison correction.

Results HER pathway DNA biomarkers were either low prevalence or nonpredictive. In expression biomarker analysis, only one gene (STXN1) was specifically associated with response to neratinib in the HER2-negative subset. In qualifying protein/phosphoprotein analyses that used reverse phase protein microarrays, six HER family markers were associated with neratinib response. After analysis was adjusted for HR/HER2 status, EGFR Y1173 (pEGFR) showed a significant biomarker-by-treatment interaction (P = .049).

The exploratory analysis of HER family signaling in patients with triple-negative (TN) disease found that activation of EGFR Y1173 (P = .005) and HER2 Y1248 (pHER2) (P = .019) were positively associated with pathologic complete response. Exploratory analysis in this pEGFR/pHER2-activated TN subgroup identified elevated levels of estrogen receptor α (P < .006) in these patients.

Conclusion Activation of HER family phosphoproteins associates with response to neratinib, but only EGFR Y1173 and STXN1 appear to add value to the graduating signature. Activation of HER2 and EGFR in TN tumors may identify patients whose diseases respond to neratinib and implies that there is a subset of patients with TN disease who paradoxically exhibit HER family signaling activation and may achieve clinical benefit with neratinib; this concept must be validated in future studies.

JCO Precis Oncol. © 2018 by American Society of Clinical Oncology
### Table A5. Bayesian Probabilities and Biomarker Prevalence for TN Population

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Probability, Neratinib &gt; Control</th>
<th>Predictive Probability of Phase III success (N = 300)</th>
<th>TN Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected TN (n = 49)</td>
<td>0.76</td>
<td>0.42</td>
<td>100</td>
</tr>
<tr>
<td>TN/EGFR Y1173-high (n = 27)</td>
<td>0.88</td>
<td>0.72</td>
<td>55</td>
</tr>
<tr>
<td>TN/HER2 Y1248-high (n = 30)</td>
<td>0.95</td>
<td>0.82</td>
<td>61</td>
</tr>
<tr>
<td>TN/EGFR Y1173-high and HER2 Y1248-high (n = 21)</td>
<td>0.99</td>
<td>0.95</td>
<td>43</td>
</tr>
</tbody>
</table>

Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative.
What Perthera Does

For the Patient

• We identify and recommend...
  • the most precisely matched therapies to oncologists and their patients
  • ranked for highest probability of best outcome

We answer the question:
“What is the best drug or drug combination for this patient?”

For Institutions

• We track the status of every patient for administrators:
  • We make sure that the most appropriate patients can use the “house” trials
  • We run the Perthera Virtual Tumor Board for every patient

We answer the question:
“How can we save money AND do better for the patient?”
Perthera Platform

• Company is run as an IRB-approved registry study.
• A real-time, patent-pending, Virtual Tumor Board.
• Proprietary algorithms power the Therapeutics Intelligence Engine and highly-curated accompanying databases.
• A closed-loop system that tracks outcomes
• User-friendly dashboards for Managers and Administrators to track and report individual or multiple patients’ status
• The system permits incremental usage of its features.
• Perthera will provide staff and/or training to ensure optimal usage of the platform.
Perthera’s Process

1. Biopsy
2. Profile
3. Analysis
4. Review
5. Report
6. Treatment
7. Data

Perthera ExpO

- Patient Biopsy
- Molecular Profiling & Patient History
- Best-In-Class Multiplex Molecular Profiling
- Fresh Biopsy & Expert Tissue Preparation (in accordance with Perthera SOP)

Clinical Knowledge

- Web Services
- Perthera Expert Oncology

Expert Medical Review

- Board-Certified Medical Review Panel

Physician’s Report

- Interpretation, Analysis, Ranked Therapies, Rationale, Clinical Trials, Drug Info, Supporting Evidence

Outcomes Data

- Patient Consultation Clinical Treatment
- Following Up and Collecting Outcomes Data

CONFIDENTIAL
The Therapeutic Intelligence Engine

~1,000,000 Molecular Data Points

~1,500 Perthera Reports Delivered

~1,000 Approved & Experimental Agents

~3,500 Drug-Gene Associations

~1,500 Drug Labels & Treatment Guidelines

~2,000 Curated Clinical Trials

~2,500 Supporting Scientific Articles

CONFIDENTIAL
An Asynchronous Cloud-Based Virtual Tumor Board Platform

Integrates molecular profiling results from all major clinical laboratories

Streamlines treatment planning & review by a panel of medical experts

Enables real-time discussion to share expertise & research findings

Perthera Report is delivered to the patient’s treating oncologist
Landmark Study Shows Precision Medicine Benefits Pancreatic Cancer Patients

Pancancer Active Network, Perthera, Inc., Published Study Finds Patients with "Actionable" Mutations Who Received Targeted Therapies Have Significantly Improved Outcomes

Jun 28, 2018, 10:53am EDT

MANHATTAN BEACH, Calif. and MCLEAN, Va., June 28, 2018 /PRNewswire-USNewswire/ -- A study published today by the Pancreatic Cancer Action Network (PanCAN), Perthera, Inc., and colleagues in the AACR Journal Clinical Cancer Research (AACR J.C.C.R.) finds that patients with "actionable" mutations who received targeted therapies have significantly improved outcomes.

Author Manuscript Published OnlineFirst on June 28, 2018; DOI: 10.1158/1078-0432.CCR-18-0531. Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Molecular Profiling of Pancreatic Cancer Patients: Initial Results from the Know Your Tumor Initiative

Michael J. Pishvaian1,2,*, R. Joseph Bender2,*, David Halverson2, Lola Rahib3, Andrew Hendifar3, Sam Mikhail4, Vincent Chung5, Vincent Picozzi6, Davendra P. S. Sohal6, Edik Blais2, Kimberly Mason2, Emily Lyons3, Lynn M. Matrisian3, Jonathan R. Brody3, Subha Madhavan1,2, Emanuel Petricoin III1,2,10

1Lombardi Comprehensive Cancer Center, Georgetown University Medical Center Washington, D.C.; 2Perthera, Inc, McLean, VA; 3The Pancreatic Cancer Action Network, Manhattan Beach, CA; 4Cedars-Sinai Medical Center, Los Angeles, CA; 5Ohio State University, Columbus, OH; 6City of Hope Cancer Center, Duarte, CA; 7Virginia Mason Medical Center, Seattle, WA; 8Cleveland Clinic, Cleveland, OH; 9The Jefferson Pancreatic, Biliary, and Related Cancer Center and the Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA. 10George Mason University, Fairfax, VA.
**Background**

The KYT (Know Your Tumor) initiative was launched in June 2014 to determine if a precision medicine approach is appropriate for pancreatic cancer. Patients are identified through the PanCAN Patient Central call center with eligibility requirements of a diagnosis of any kind of pancreatic malignancy, available tumor tissue and adequate time before the next treatment decision. Panthera obtains patient consent under an IRB-approved observational registry study, coordinates molecular testing through external laboratories, convenes a virtual molecular tumor board consisting of medical experts in precision oncology and pancreatic cancer, prepares a ranked list of therapy options based on the patient’s clinical characteristics, treatment history, and molecular profiling results. Real-world outcomes are then collected after delivering a report to the patient’s cancer care team.

**Patient Accrual**

<table>
<thead>
<tr>
<th>1601 KYT Referrals (all pancreatic cancer subtypes)</th>
<th>7th % in process</th>
<th>46% patients consented (80% of referrals to Panthera)</th>
<th>25% in process</th>
<th>46% hold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1112 Patients Biopsied (77% of consented patients)</td>
<td>137% in process</td>
<td>100% of biopsied patients</td>
<td>137% in process</td>
<td>100% of biopsied patients</td>
</tr>
<tr>
<td>986 Perthera KYT Reports (86% of biopsied patients)</td>
<td>137% in process</td>
<td>33% of biopsied patients in prior therapy</td>
<td>241 initiated new treatment(s) post-report</td>
<td>185 implemented a report-listed therapy option (77%)</td>
</tr>
</tbody>
</table>

**Multi-Omics Profiling Results & Actionability Assessment**

<table>
<thead>
<tr>
<th>NGS testing was primarily performed by Foundation Medicine (75%) IHC testing was typically performed by Caris or NeoGenomics</th>
</tr>
</thead>
</table>

*Highly Actionable* findings

<table>
<thead>
<tr>
<th>BRAF</th>
<th>V600Emutation</th>
<th>Gains in BRAF</th>
<th>Losses in BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF10</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>FGFR3</td>
<td>1%</td>
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<td>FGFR4</td>
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<td>FGFR5</td>
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<td>FGFR6</td>
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<tr>
<td>FGFR11</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td>FGFR12</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
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</table>

**Patient Impact**

**SUSAN**

- **Not her real name:** BRCA2 mutation. 57 YO diagnosed with metastatic PDAC 2013. Received FGF and FX. Enrolled in KYT 1/16: BRCA2 alteration. Received first agent, pegelatib as third line therapy. Insurance coverage after approval. 16 mos PFS (discontinued).

**JOE**

- **Not her real name:** BRCA2 mutation & ALK protein overexpression. 72 YO diagnosed with metastatic PDAC 2013. Received FXG and FXA. Enrolled KYT 2/16. No response to carboplatin clinical trial. PARP inhibitor and mCDK4 in 4th line, 9 Mos PFS (discontinued).

**GAI**

- **Not her real name:** NTRK4-ETV6 fusion. 71 YO diagnosed with PNET 3/16. Resistant, adjuvant Cis/tiposide. Recurrence b with irinotecan. Enrolled in KYT 5/17. Enrolled in a clinical trial with a selective NTRK inhibitor. 16 Mos PFS (ongoing).

**DAVID**


**LEILA**

- **Not her real name:** BRAF V600E. 62 YO diagnosed with metastatic pancreatic carcinoma, high grade, with neuroendocrine and acinar cell features 2/16. Started 1st line FOLFIRINOX. Enrolled in KYT 7/16. Started 2nd line dabrafenib + trametinib. 10 mos PFS (discontinued).

**Conclusion**

A precision medicine approach to pancreatic cancer is feasible across the US and can result in a statistically significant increase in progression free and overall survival.

**KYT Status**

- 836 reports completed
- 88% successful biopsies
- 35% from community physicians
- 48 states

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**Image References:**

- PanCAN KPT: © PanCAN
- Perthera Report & Panel: © Perthera, Inc.
- Therapeutic Intelligence Engine: © Perthera, Inc.
- June 2018: © Perthera, Inc.
Patient Accrual

1681 KYT Referrals (all pancreatic cancer subtypes)
- 0 in process
- 0 on hold

1435 Patients Consented (85% of referrals to Perthera)
- 4 in process
- 6 on hold

1112 Patients Biopsied (77% of consented patients)
- 25 in process
- 4 on hold

986 Perthera KYT Reports (89% of biopsied patients)
- 137 in process
- 329 continuing prior therapy

241 Initiated New Treatment(s) Post-Report
- 185 implemented a report-listed therapy option (77%)
- 56 implemented only non-report-listed therapies (23%)

246 Closed Pre-Consent
- 90 unable to contact
- 43 patient unsupportive
- 28 doctor unsupportive
- 15 unable to biopsy
- 10 cost/insurance
- 17 health concerns
- 18 deceased

313 Closed Pre-Biopsy
- 76 unable to contact
- 35 patient unsupportive
- 41 doctor unsupportive
- 22 unable to biopsy
- 2 cost/insurance
- 21 health concerns
- 89 deceased

97 Closed Pre-Report
- 17 unable to contact
- 6 patient unsupportive
- 3 doctor unsupportive
- 7 unable to re-biopsy
- 7 health concerns
- 56 deceased

279 Closed Pre-Utilization
- 107 unable to followup
- 149 deceased/hospice
Highly Actionable (Matched)
Highly Actionable (Unmatched)
No Highly Actionable Findings

p-value = 0.0287

p-value = 0.0057
How I-SPY 2 Works

I-SPY 2 breaks from the traditional randomized clinical trial model, employing an 'adaptive' clinical trial model designed to increase trial efficiency by minimizing the number of participants and time required to evaluate an experimental agent.

At consent, a new participant's breast cancer is classified into one of 10 molecular subtypes. Then, for each participant in the trial:

1) I-SPY 2's adaptive randomization engine assigns a participant to a study arm; it gives greater weight to arms that have been successful in the participant's tumor subtype.

2) The endpoint is assessed at time of surgery. Primary endpoint is RCB 0 or pathologic complete response meaning the tumor has disappeared completely.

3) Based on the participant's tumor subtype, outcome (i.e. MRI volume, pCR) and treatment received, the predictive probabilities of the agent in the various subtypes are updated in real time.

4) If predictive probabilities for an experimental agent reach a pre-determined level of efficacy in one or more molecular subtypes, it is declared a success ("graduates"). Alternatively, it may be stopped for futility after reaching a maximum number of participants. At any point new agents can enter the trial through a protocol amendment.

5) The participant's serial MRI measures, RCB scores and tumor subtype are used to update the prior probabilities of the randomization engine -- over time this refines the targeting of subsequent participants.
Efficiency Bred From Innovation

The success of the I-SPY 2 trial is not simply the result of a single innovation in trial design. It is the result of a pain-staking deconstruction and re-engineering of the entire clinical trial enterprise, from protocol development through registration.

- **Early Endpoint**
  - I-SPY 2's early surrogate efficacy endpoint (pCR) gets results faster

- **Adaptive Design**
  - Adaptive randomization makes the most of every patient enrolled

- **Real-World Control**
  - A common control arm as comparator, with a decade of historical data

- **Curable Population**
  - A breast cancer population where standard of care has much room to improve

- **Neoadjuvant Model**
  - Systemic therapy first lets you see how tumors respond to treatment

- **Multiple Agents**
  - Up to 6 agents can be efficiently, independently evaluated in parallel

- **Biological Targeting**
  - Randomization targets agents to more responsive molecular subtypes

- **Master Protocol**
  - Less paperwork means vastly compressed start-up times by 3-4 months

- **Serial MRI**
  - Optimized imaging protocols quantify tumor response over time

- **Biomarker Discovery**
  - Integrated platform for companion biomarker discovery

- **Active QC**
  - Enterprise-wide process standardization with frequent re-certification
INDIVIDUALIZED THERAPY OF METASTATIC CANCER
SIDE OUT TRIAL  Molecular profiling for individualized therapy of metastasis

- Biopsy of Metastasis
- Laser Capture Microdissection
- Molecular Profiling
- Select Therapy
Primary Objective of the Study

1. To compare progression free survival (PFS) using therapy selected by molecular profiling (period B) with PFS for the most recent therapy on which the patient has just progressed (period A)

- If $\text{PFS}_B / \text{PFS}_A$ ratio $\geq 1.3$ then MP selected therapy was defined as having benefit for patient

Compare new patient value to existing population data for phospho EGFR values

**PHYSICIAN REPORT**

**PATIENT A**

<table>
<thead>
<tr>
<th>DRUG TARGET</th>
<th>ACTIVITY LEVEL</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospho-EGFR</td>
<td>3+</td>
<td>TARCEVA</td>
</tr>
<tr>
<td>Phospho-c-KIT</td>
<td>1+</td>
<td>GLEEVEC</td>
</tr>
<tr>
<td>Phospho-VEGF</td>
<td>3+</td>
<td>AVASTIN</td>
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<tr>
<td>Phospho-mTOR</td>
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**PATIENT B**

<table>
<thead>
<tr>
<th>DRUG TARGET</th>
<th>ACTIVITY LEVEL</th>
<th>DRUG</th>
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</thead>
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<tr>
<td>Phospho-EGFR</td>
<td>0</td>
<td>TARCEVA</td>
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<tr>
<td>Phospho-c-KIT</td>
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<td>GLEEVEC</td>
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<tr>
<td>Phospho-VEGF</td>
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<td>AVASTIN</td>
</tr>
<tr>
<td>Phospho-mTOR</td>
<td>2+</td>
<td>TORISEL</td>
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</tbody>
</table>
# GMU Pathway Mapping Assay Report

**Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patient’s Profiles: Relative Levels of Drug Target Activation</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Target from FDA Approved Package Insert</strong></td>
<td><strong>Substrate for Cytoplasmic Drug Targets from FDA Approved Package Insert</strong></td>
<td><strong>Downstream Inhibitor of Drug Target Activity</strong></td>
</tr>
<tr>
<td>Tarceva</td>
<td>p. EGFR (Y1175)</td>
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</tr>
<tr>
<td></td>
<td>p. erbB2 (Y1248)</td>
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<tr>
<td>Herceptin</td>
<td>p. EGFR p. erbB2 (Y1248)</td>
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<td>PTEN</td>
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<tr>
<td>Tykerb</td>
<td>p. AK (Y1208)</td>
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<tr>
<td>Xanok</td>
<td>p. PDK4 p. c-Akt (Y765)</td>
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<td></td>
<td>p. erbB2</td>
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<tr>
<td>Sutent</td>
<td>p. PDK4 p. c-Akt (Y765)</td>
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<td></td>
<td>p. erbB2</td>
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<tr>
<td>Nefnavir</td>
<td>p. PDK4 p. c-Akt (Y765)</td>
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<td>p. Akt</td>
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<td>Telgiene</td>
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<td>Sprycel</td>
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<tr>
<td>Toralbistin</td>
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<td>p. erbB2</td>
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<tr>
<td>Proliferation Marker</td>
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</table>

**Notes:**
- This information is provided for research purposes only.
- This information cannot be considered as diagnostic of any disease state.
- This information is not a recommendation for treatment.

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**GMU CAPMM Medical Director: Lance Liotta, MD, PhD**

This assay is not cleared or approved by the US FDA, and has been generated in a laboratory setting that is compliant with the Clinical Laboratory Improvement Amendments of 1988 (CLIA).
Comparison of PFS on MP therapy vs. PFS on prior therapy for 13 patients with GMI of ≥ 1.3

RPMA Results

<table>
<thead>
<tr>
<th>Drug Target(s)</th>
<th>EGFR Y1173</th>
<th>Erb2 Y1248</th>
<th>VEGFR Y996</th>
<th>PDGF Y751</th>
<th>mTOR S2481</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cKit Y719</td>
<td>cAbl T735</td>
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<tr>
<td>Downstream</td>
<td>ERK</td>
<td>ERK</td>
<td>ERK</td>
<td>ERK</td>
<td>p70S6K389</td>
</tr>
<tr>
<td>Substrate from Drug Target</td>
<td>T202/Y204</td>
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<td>T202/Y204</td>
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<tr>
<td></td>
<td>AKT S473</td>
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<tr>
<td>Number of</td>
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<td>3/25</td>
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</tr>
<tr>
<td>Pathway Activated</td>
<td>(52.0%)</td>
<td>(12.0%)</td>
<td>(12.0%)</td>
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<tr>
<td>Positive Patients</td>
<td></td>
<td></td>
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Molecular profile was not available for 3 of the 25 patients due to inadequate material