Genome Directed Cancer Treatment

Use Case for a Learning Cancer System

March 23, 2012

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Director Cancer Clinical Informatics, Vanderbilt Ingram Cancer Center
Assistant Professor of Biomedical Informatics and Medicine
Biomarkers in the Clinical Continuum

- **Diagnosis**
  - Risk Biomarker
  - Diagnostic Biomarker

- **Treatment Selection**
  - Prognostic Biomarker
  - Predictive Biomarker

- **Treatment Plan Management**

- **Treatment Response Assessment**
  - Response Biomarker
Personalized Cancer Medicine Initiative

 Genome directed cancer treatment selection

Diagnosis → Treatment Selection → Treatment Plan Management → Treatment Response Assessment

Predictive Biomarker
Traditional View of Cancer

Melanoma

- Arising from Skin Without Chronic Sun Damage
- Arising from Skin With Chronic Sun Damage
- Arising from Mucosal Surfaces
- Arising from Acral Surfaces

Lung Cancer

- Adeno-carcinoma
- Squamous
- Large
- Small
Vanderbilt-Ingram Cancer Center
Personalized Cancer Medicine Initiative

7/1/10-12/31/11

Melanoma Panel: 538 patients
67% Patients with Actionable Mutation
33% No Mutation Identified

- No Mutation 33.0%
- NRAS 19.0%
- GNAQ 2.5%
- BRAF 40.5%
- GNA11 1.0%
- CTNNB1 1.0%
- KIT 3.0%

Lung Panel: 451 patients
46% Patients with Actionable Mutation
54% No Mutation Identified

- No Mutation 54%
- EGFR 17%
- ERBB2 1%
- KRAS 21%
- BRAF 3%
- PIK3CA 3%
- NRAS 0.25%
- PTEN 0.25%
- MEK 0.5%
- 12 ALK fusions
Old Method for Reporting Mutation Results in the Electronic Medical Record

Old Method:

• Report Template
• Scanned into Electronic Health Record as image file (not computable)

Challenges:

• How to report > 40 mutations in 8 genes?
• Whose role to curate knowledge regarding clinical significance?
• Lack clinical trial information

The epidermal growth factor receptor (EGFR) gene, mapped to 7p12, encodes a transmembrane glycoprotein that is a member of the protein kinase superfamily. EGFR protein is expressed on the cell surface and as a receptor, binds to epidermal growth factor (EGF). The protein-ligand interaction induces receptor dimerization and tyrosine autophosphorylation resulting in cell proliferation. Somatic mutations in the tyrosine kinase-binding domain of the EGFR gene are associated with non-small cell lung carcinoma, primarily moderately to well-differentiated adenocarcinoma. EGFR mutations have been observed in approximately 10% of lung adenocarcinomas in patients from the United States and are significantly associated with Asian ethnicity, female gender and never-smokers.

ERBB2 is a member of the EGF family of receptor tyrosine kinases and plays important roles in the pathogenesis of several human cancers. Somatic mutations in the form of in-frame duplications and/or insertions in a small stretch of exon 20 have been reported in non-small cell lung carcinomas. Of interest, exon 20 insertion mutations in ERBB2 or EGFR are significantly more prevalent in the same subpopulations in which other EGFR mutations occur.

Progressive and/or metastatic non-small cell lung carcinomas can be treated with inhibitors of the EGFR receptor. Somatic mutations in the tyrosine kinase domain of the EGFR gene present in lung adenocarcinomas can affect a patient’s response to EGFR inhibitors. 90% of EGFR mutations in this population include short in-frame deletions in exon 19 and a T > G point mutation in exon 21 at codon 858 (L858R). The presence of either mutation correlates with sensitivity to EGFR inhibitors. Conversely, insertion mutations in exon 20 of either ERBB2 or EGFR gene appear to be less responsive to therapy.

DNA extracted from this patient’s tumor was amplified for EGFR exons 19 and 20 and ERBB2 exon 20 using multiplex fluorescent PCR to detect small deletions or insertions. Detection of mutation L858R was performed using fluorescent PCR coupled with restriction endonuclease digestion with Sau96I. All amplicons were analyzed using capillary electrophoresis. An in-frame deletion in exon 19 of the EGFR gene was detected.

In summary, the results of this study demonstrate that this patient does have an exon 19 deletion of the EGFR gene. The presence of this mutation indicates that this tumor will likely be responsive to EGFR inhibitors. It is important to note that this assay is specific for these four mutations and does not rule out the presence of other EGFR or ERBB2 mutations that may be present but not detected by this assay and which may affect treatment response.
<table>
<thead>
<tr>
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<th>Patient Name</th>
<th>Actions</th>
<th>Tumor Gene Mutations</th>
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<td>03</td>
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<td></td>
<td>B</td>
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<td>03</td>
<td>56 A, P</td>
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<td>B</td>
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<td>35 B, J A</td>
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<td>77 G, T</td>
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<td>73 H, A</td>
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<td>03</td>
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<td>79 S, A S</td>
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<td>02</td>
<td>40 W, J E I</td>
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<tr>
<td>03</td>
<td>74 W, C L</td>
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**Order Status (letter):**
- O = Order Received
- R = Outside Specimen Requested
- A = Outside Specimen Arrived
- v = Specimen Accessioned

**Result Status (colored box):**
- Yellow = Gene Mutation Detected
- Grey = Gene Mutation Not Detected
- Red = No Result – Insufficient Specimen
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- **BRAF c.1798_1799GT>AG (V600R)** Not Detected
- **BRAF c.1798_1799GT>AA (V600K)** Not Detected
- **BRAF c.1799T>A (V600E)** Detected
- **BRAF c.1799_1800TG>AA (V600E)** Not Detected
- **BRAF c.1798G>A (V600M)** Not Detected
- **BRAF c.1799T>G (V600G)** Not Detected
- **BRAF c.1799_1800TG>AT (V600D)** Not Detected
BRAF V600E (c.1799T>A) mutation in Melanoma

**BRAF V600E mutation**

**Properties**
- Location of mutation: Kinase domain (exon 15)
- Frequency of BRAF V600E: ~85-90% of BRAF mutant melanoma

**Implications for Targeted Therapeutics**
- Response to BRAF inhibitors: Confers increased sensitivity*
- Response to MEK inhibitors: Uncertain at this time
- Response to KIT inhibitors: Uncertain at this time

The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a Glutamic acid (E). This mutation occurs within the activation segment of the kinase domain (Fig. 2). Approximately 70-90% of V600 BRAF mutations are V600E (Rubinstein, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2002). BRAF mutations are usually found in tumors wildtype for NRAS, KIT, and other driver mutations.

*In the initial phase I trial, patients with metastatic melanoma whose tumor harbored a BRAF V600E mutation displayed an initial response rate to vemurafenib (PLX4032), an orally available inhibitor of mutated BRAF. The estimated progression-free survival was >7 months and overall survival had not been reached at the time of study publication (Fehlings, 2010). In the follow-up randomized phase III trial comparing vemurafenib to dacarbazine in previously untreated, metastatic melanoma with the BRAF V600E mutation, vemurafenib improved rates of overall survival and progression-free survival (Chapman, 2011).

*Pre-clinical data has correlated the presence of activating mutations in BRAF with sensitivity to non-ATP competitive MEK inhibitors, AZD6244 and CI-1040 (Davies, 2007; Sotol, 2006). In a Phase II clinical trial of AZD6244 versus temozolomide, 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Gumer, 2008).

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<thead>
<tr>
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<th>Treatment Agent</th>
<th>Drug Class</th>
<th>Line of Treatment</th>
<th>n pts in study</th>
<th>Response Rate</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Level of evidence</th>
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<tr>
<td>vemurafenib (PLX4032)</td>
<td>Mutated BRAF TKi</td>
<td>1st to 3rd</td>
<td>32</td>
<td>81%</td>
<td>&gt;7 months (estimated)</td>
<td>Not reached</td>
<td>III-1</td>
<td>(Fehlings, 2010)</td>
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BRAF V600E (c.1799T>A) mutation in Melanoma

**Properties**

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**Implications for Targeted Therapeutics**

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AZD6244 versus temozolomide: 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Chapman, 2011).

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*To be confirmed by further studies**
### BRAF V600E mutation

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**Note:** BRAF V600E mutation can lead to resistance and requires combined target therapy. Clinical trials have shown mixed responses (12% objective response rate) (Gutierrez, 2008).

### BRAF c.1799T>A (V600E) mutation in Melanoma

**Properties**
- Location of mutation: Kinase domain (exon 15)
- Frequency of BRAF V600E: ~85-90% of BRAF mutant melanoma

**Implications for Targeted Therapeutics**
- Response to BRAF inhibitors: Confers increased sensitivity*
- Response to MEK inhibitors: Uncertain at this time*
Inhibition of mutated, activated BRAF in metastatic melanoma.


Abramson Cancer Center of the University of Pennsylvania, Philadelphia, USA. kflaherty@partners.org

Abstract

BACKGROUND: The identification of somatic mutations in the gene encoding the serine-threonine protein kinase B-RAF (BRAF) in the majority of melanomas offers an opportunity to test oncogene-targeted therapy for this disease.

METHODS: We conducted a multicenter, phase 1, dose-escalation trial of PLX4032 (also known as RG7204), an orally available inhibitor of mutated BRAF, followed by an extension phase involving the maximum dose that could be administered without adverse effects (the recommended phase 2 dose). Patients received PLX4032 twice daily until they had disease progression. Pharmacokinetic analysis and tumor-response assessments were conducted in all patients. In selected patients, tumor biopsy was performed before and during treatment to validate BRAF inhibition.

RESULTS: A total of 55 patients (49 of whom had melanoma) were enrolled in the dose-escalation phase, and 32 additional patients with metastatic melanoma who had BRAF with the V600E mutation were enrolled in the extension phase. The recommended phase 2 dose was 960 mg twice daily, with increases in the dose limited by grade 2 or 3 rash, fatigue, and arthralgia. In the dose-escalation cohort, among the 16 patients with melanoma whose tumors carried the V600E BRAF mutation and who were receiving 240 mg or more of PLX4032 twice daily, 10 had a partial response and 1 had a complete response. Among the 32 patients in the extension cohort, 24 had a partial response and 2 had a complete response. The estimated median progression-free survival among all patients was more than 7 months.

CONCLUSIONS: Treatment of metastatic melanoma with PLX4032 in patients with tumors that carry the V600E BRAF mutation resulted in complete or partial tumor regression in the majority of patients. (Funded by Plexxikon and Roche Pharmaceuticals.)
BRAF V600E (c.1799T>A) mutation in Melanoma

**BRAF V600E mutation**

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**Implications for Targeted Therapeutics**

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**BRAF V600E mutation**

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BRAF Mutation Directed Melanoma Clinical Trials

Great effort was made to include all clinical trials relevant for this mutation. However, the completeness of this information cannot be guaranteed.

At Vanderbilt (4)

<table>
<thead>
<tr>
<th>Protocol No.</th>
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<tr>
<td>VICCPHI1075</td>
<td>A Phase Ib, Open Label, Dose-Escalation, Study Evaluating the Safety, Tolerability and Pharmacokinetics of RO5185426 in Combination with GDC-0973 when Administered in Patients with BRAFV600E-Positive Metastatic Melanoma Who Have Progressed After Treatment with RO5185426</td>
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<tr>
<td>06/01/2011</td>
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<tr>
<td>VICCMEL1091</td>
<td>BRF113929: A Phase II Open-Label, Two-Cohort, Multicentre Study of GSK2118436 as a Single Agent in Treatment Naive and Previously Treated Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain</td>
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<tr>
<td>VICCPHI1076</td>
<td>A Phase I, Randomized, Open-Label, Multi-Center, Two Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960mg RO5195426 Twice Daily to BRAF-V600E Positive Metastatic Melanoma Patients</td>
</tr>
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<tr>
<td>VICCMEL1083</td>
<td>An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma</td>
</tr>
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<td>Pending</td>
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Melanoma Clinical Trials at Vanderbilt (7)

Tennessee (4)

United States (13)

Internationally (12)
**BRAF Mutation**

**Clinical Trial VICCphi1075**

**Title**
A Phase Ib, Open Label, Dose-Escalation, Study Evaluating the Safety, Tolerability and Pharmacokinetics of RO5185426 in Combination with GDC-0973 when Administered in Patients with BRAFV600E-Positive Metastatic Melanoma Who Have Progressed After Treatment with RO5185426

**Principal Investigator(s)**
Igor Puzanov

**Description**
The purpose of this study is to test the combination of the investigational drugs RO5185426 (BRAF inhibitor) and GDC-0973/XL518 (MEK inhibitor) in order to find a safe and tolerated dose when taking these drugs together.

**Eligibility**

**Details**

**Learn more**
- Call toll-free number: 1-800-811-8480
- Visit [Online self-referral form](#)
- Print this page for your doctor

**Melanoma (4)**

**Tennessee (4)**

**United States (13)**

**Internationally (12)**
## BRAF Mutation Directed Melanoma Clinical Trials

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<tr>
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<td>A Study of RO5185426 And GDC-0973 in Patients With BRAF-Mutation Positive Metastatic Melanoma</td>
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<tr>
<td>NCT01350401</td>
<td>Phase I/II Study to Assess the Safety and Activity of Enhanced TCR Transduced Autologous T Cells in Metastatic Melanoma</td>
</tr>
<tr>
<td>NCT01390818</td>
<td>Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors</td>
</tr>
<tr>
<td>NCT01136967</td>
<td>An Open-Label, 2-Cohort, Multicenter, Study of E7080 in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma</td>
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<tr>
<td>NCT00866177</td>
<td>Phase II Study of MEK Inhibitor AZD6244 in Patients With BRAF-Mutated or NRAS-Mutated, Unresectable Stage III or IV Melanoma</td>
</tr>
<tr>
<td>NCT00948467</td>
<td>Study of TAK-733 in Adult Patients With Advanced Nonhematologic Malignancies</td>
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<tr>
<td>NCT01248936</td>
<td>A Study of RO5185426 in Patients With Metastatic Melanoma</td>
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<td>NCT01266967</td>
<td>A Study of GSK2118436 in BRAF Mutant Metastatic Melanoma to the Brain</td>
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<tr>
<td>NCT01072175</td>
<td>Investigate Safety, Pharmacokinetics and Pharmacodynamics of GSK2118436 &amp; GSK1120212</td>
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</tbody>
</table>

#### Internationally (12)
Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors

This study is currently recruiting participants.
Verified on July 2011 by EMD Serono
First Received on April 18, 2011. Last Updated on July 8, 2011

Purpose
This research trial is testing a combination of two experimental drugs, MSC193636B (Mitogen-activated protein extracellular signal-regulated kinase (Mek) Inhibitor) and SAR245409 (Phosphatidylinositol 3-kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) inhibitor), in the treatment of locally advanced or metastatic solid tumours. The primary purpose of the study is to determine the maximum tolerated dose of the drug combination.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally Advanced Solid Tumor</td>
<td>Drug: MSC193636B and SAR245409</td>
<td>Phase I</td>
</tr>
<tr>
<td>Metastatic Solid Tumor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-Label, Phase Ib Dose Escalation Trial of Oral Combination Therapy With MSC193636B and SAR245409 in Subjects With Locally Advanced or Metastatic Solid Tumors

Resource links provided by NLM:
- MedlinePlus related topics: Cancer
- Drug Information available for: Sirolimus, Everolimus, CCI 779
- U.S. FDA Resources

Further study details as provided by EMD Serono:
My Cancer Genome

Genetically informed cancer medicine - the next standard of care

Find a Cancer Mutation

Select Disease

Select disease and within that disease and

Select gene

Select gene within that disease and

Select gene-variant

GO

7 Cancers
Lung
Melanoma
Breast
Colon
Thymic
GIST
Thyroid

22 Genes

203 Disease-Gene-Variant Relationships
NEW clinical trial search
- 135 Cancer Diagnoses
- 443 Cancer Genes
>1500 site visits per week

53,515 visits came from 120 countries and territories
This country/territory sent 30,308 visits via 52 regions
Worldwide Collaboration

- 30 Contributors
- 13 Institutions
- 6 Countries
Scale, Maintain & Sustain

Content Generation → My Cancer Genome → Content Dissemination
Decision Support as a Service

- Vanderbilt EHR
- Public Access
- Treatment Plan Selection
- Laboratory Testing Facility
- Academic Medical Center EHR
- Oncology Vendor EHR
Scalability: Data Driven Approach

Assess clinical outcomes → Select patient treatment

Compare treatment effectiveness → Implement new evidence for treatment prioritization

Learning Cancer System
Learning Cancer System

- Diagnosis
  - Primary Site
  - Histology
  - Stage
  - Biomarkers

- Treatment Selection

- Treatment Plan Management
  - Treatment History

- Treatment Response Assessment
  - Tumor Response
    - Quality of Life
    - Toxicity
    - Survival

Aggregate & Analyze
Case Reports: Manual Annotation

DIRECT

• Collection of EGFR mutations in NSCLC
• 1596 patient level case reports
  • 1876 gene, drug, response instances
• 146 publications
• 150 unique primary EGFR mutations
• 47 unique secondary EGFR mutations

L Horn, H Chen, CM Lovly, J Andrews, P Yeh, MA Levy, W Pao
Case Reports: Automated Extraction

- Labs, notes, medications
  - Vanderbilt EHR: 1.8M pt
  - Tumor Registry: 63K pt
  - Site, Stage, histology, vital status

De-identification

Synthetic Derivative

Continuous extraction and integration with knowledge resources

>1000 pt with tumor gene mutation analysis and growing
Chemotherapy Plan Abstraction Method

Medication Event Extraction → Chemotherapy Plan Abstraction → Cohort Plan Analysis
Data Quality: Extracting Medication Events

EHR Data Sources

- Physician Notes (100s)
- Physician Orders (100s-1000s)
- Pharmacy Dispensing Records (100s-1000s)
- Nurse Administration Records (100s-1000s)

Free Text

Structured

Data Accuracy

Truthfulness – Event Accuracy

+ + +

+ + +

+ + +

+ + +
Data Completeness

Friedman 2010
Triangulation of Data Sources

Event Triangulation

Terminology Mapping

Data Extraction Methods

Data Sources

Probability of Medication Event X(t)

- Medication Event X(t)
  - NLP Machine Learning
  - Notes

- Medication Event X(t)
  - Transaction System Data Processing
  - Orders

- Medication Event X(t)
  - Pharmacy

- Medication Event X(t)
  - Nursing
Structured and free-text Format
Chemotherapy Medication Events at VUMC

- Clinical Notes: 100%
- Orders: 95%
- Pharmacy Dispensing Records: 100%
- Nurse Admin Records: 95%

Data source:
- Free-text
- Structured
Vanderbilt-Ingram Cancer Center

Pharmacy and Tumor Registry Data

**Pharmacy Dispensing Records**
Jan. 2006 – May 2011

- Patients: 487K
- Chemo: 8,278

**Tumor Registry**

- 5,394 medication events
- 63K patients

- Chemo: 213K
Chemotherapy Plan Abstraction Method

Medication Event Extraction → Chemotherapy Plan Abstraction → Cohort Plan Analysis

Recall 89.9
Precision 75.5
Accuracy 69.6

Bhatia, Levy, AMIA 2011
## Cohort analysis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patient Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide, Doxorubicin</td>
<td>198</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>138</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>61</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>55</td>
</tr>
<tr>
<td>Cyclophosphamide, Docetaxel</td>
<td>48</td>
</tr>
</tbody>
</table>

---

Breast Cancer Patient Cohort  
\( n = 554 \)  
Unique Plans = 107
Cohort analysis

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Patient Count</th>
<th>Periodicity (days)</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide, Doxorubicin</td>
<td>198</td>
<td>~15.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>138</td>
<td>~14.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Breast Cancer Patient Cohort
n=554
Unique Plans = 107
Summary

• Genome directed cancer treatment is a driving use case for learning cancer systems

• EMR data may be used for such a system

• EMR data quality may be mitigated through triangulation of multiple sources
Acknowledgements

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• Dario Giuse
• Jonathan Grande
• RuAnn Schleicher
• Jay Cowan
• Michael Assink
Thank you
Method Performance

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Patient Level Plans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern Recognition</td>
<td>Refined Plans</td>
</tr>
<tr>
<td>KB</td>
<td></td>
</tr>
</tbody>
</table>

Manually annotated plans used as Gold Standard

Patients - 7,805
Med. events – 139,659

<table>
<thead>
<tr>
<th></th>
<th>Training</th>
<th>Test1</th>
<th>Test2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>163</td>
<td>341</td>
<td>168</td>
</tr>
<tr>
<td>Med. events</td>
<td>2,298</td>
<td>5,713</td>
<td>3,214</td>
</tr>
</tbody>
</table>

- **Recall**: 88.8, 91.3, 89.9
- **Precision**: 75.2, 82.9, 75.5
- **Accuracy**: 68.7, 76.8, 69.6