Cancer Genomics Program at the Princess Margaret Cancer Centre

Beyond the Genetic Prescription Pad: Personalizing Cancer Medicine in 2014

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Division of Medical Oncology & Hematology
Bras Drug Development Program
Learning Objectives

• To introduce the Princess Margaret Cancer Centre Cancer Genomics Program

• To provide a rationale for genotyping advanced solid tumours

• To review the early Princess Margaret Cancer Centre experience with clinical genotyping and drug matching
Cancer Genomics Program (CGP)

• Focus is clinical characterization of genetic mutations and molecular mechanisms that drive individual patient’s cancer

• Mission of the CGP =
  - To advance personalized cancer medicine
  - To improve prognostication
  - To match patients to targeted therapies based on their genotype
Clinical Considerations for Cancer Genomics

- Archival or Fresh Biopsy
- Testing Platform
- Laboratory Certification
- Patient Selection
- Results Reporting
- Data Interpretation
Princess Margaret Integrated Molecular Profiling in Advanced Cancers Trial (IMPACT)

- Patients with selected advanced solid tumors receiving treatment at Princess Margaret
  - Breast, colorectal, gynecological, NSCLC, upper aerodigestive tract, pancreatobiliary, and genitourinary
  - Other tumor types referred for phase I trials

- Formalin–fixed paraffin–embedded archival tissue available for molecular testing
  - Tumor block or 15 unstained slides + H&E slide

- Age ≥ 18 years, able to provide informed consent

Bedard PL et al. ASCO 2013; abstract 11002
IMPACT Study Schema

First Patient First Visit
March 1, 2012

Patient

Clinician

FFPE Tissue Collection

Molecular Screening

CAP/CLIA Molecular Diagnostics Laboratory
Sequenom Genotyping and/or Targeted MiSeq NGS
Mutation Verification

Interpretation and treatment recommendation

Final profiling report

Pathology Review

Tumor DNA

Tumor Sample

DNA extraction

Tissue processing

Archival Tumor & Blood Sample

Consent and screening
Princess Margaret Sequenom Solid Tumor Panel

- SNP Genotyping 23 genes for 279 mutations (hotspots – substitutions and insertions/deletions)

<table>
<thead>
<tr>
<th>Gene</th>
<th>(No. of mutations)</th>
<th>Gene</th>
<th>(No. of mutations)</th>
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<tbody>
<tr>
<td>AKT1</td>
<td>(1)</td>
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<td>AKT2</td>
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<td>KRAS</td>
<td>(16)</td>
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<td>AKT3</td>
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<td>(12)</td>
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<tr>
<td>HRAS</td>
<td>(13)</td>
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# Patient Characteristics

## Patients Enrolled

<table>
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<tbody>
<tr>
<td>Enrollment Period</td>
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<tr>
<td>Median Age (range)</td>
</tr>
<tr>
<td>Male/Female</td>
</tr>
<tr>
<td>Median prior lines of treatment (range)</td>
</tr>
<tr>
<td>ECOG performance status (0/1/2)</td>
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</table>

## Primary Site

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Breast</td>
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<tr>
<td>Colorectal</td>
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<tr>
<td>Gyne</td>
</tr>
<tr>
<td>NSCLC</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

[Pie chart showing distribution of primary site]
<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>Screen Failure (%)</td>
<td>75 (11%)</td>
</tr>
<tr>
<td>Median DNA quantity (range)</td>
<td>3,600ng (18 – 39,060ng)</td>
</tr>
<tr>
<td>Median time for pathology review</td>
<td>1.1 weeks</td>
</tr>
<tr>
<td>Median time for genotyping</td>
<td>5.3 weeks</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients Genotyped by Sequenom</th>
<th>Patients with Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
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<tr>
<td>Colorectal</td>
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<td></td>
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<tr>
<td>NSCLC</td>
<td></td>
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<tr>
<td>Gyne</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

176/421 Patients Genotyped with $\geq 1$ Mutations (42%)
## Matched Treatment to Genotype

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median follow-up from reporting (range)</td>
<td>7.0 months (0 – 14)</td>
</tr>
<tr>
<td>Patients receiving treatment matched to genotype (% of patients with mutations)</td>
<td>43 (24%)</td>
</tr>
<tr>
<td>Patients enrolled in clinical trials matched to genotype (% of patients matched)</td>
<td>23 (53%)</td>
</tr>
<tr>
<td>Number of trial enrollments</td>
<td>25</td>
</tr>
</tbody>
</table>

### Patients Matched to Clinical Trials

- **Pancreas**: 1
- **Small Bowel**: 1
- **Breast**: 5
- **NSCLC**: 7
- **Colorectal**: 1
- **Endometrial**: 1
- **Ovarian**: 7
Best Tumor Shrinkage of Target Lesions
Patients Matched To Clinical Trials

N=21

Primary Site of Cancer

- breast
- colorectal
- NSCLC
- ovarian
- other

* Confirmed partial response RECIST v1.1

- EGFR
- ERBB2
- KRAS
- NRAS
- PIK3CA

mutant
wild type
IMPACT Accrual
(as of January 31/14)
Community Oncology
Molecular Profiling in Advanced Cancers Trial

- Access to molecular profiling for patients receiving treatment at other Ontario hospitals
- Improve enrolment in mutation-specific clinical trials
- Up to 500 patients/year
- First clinic launched November 16, 2012
Community Oncology Molecular Profiling in Advanced Cancers Trial (COMPACT)

- Access to molecular profiling for patients treated at other Ontario hospitals
- Improve enrolment to mutation-specific trials at Princess Margaret
- Referral from community medical oncologists
  - advanced breast, colorectal, gynecological, and non-small cell lung cancer on standard treatment
- Patients seen at COMPACT clinic for assessment, consent and blood sample collection
Initial Greater Toronto Area Launch
Perspectives of Community Oncologists

• Semi-structured interviews with 17 medical oncologists from 8 Ontario hospitals

• Optimism for long term benefits

• Concerns access to relevant trials, knowledge limitations, and transitions between hospitals

• Need to improve patient understanding, manage expectations, and communication of germline findings

Tan DSP et al. CCRC 2013
Communication with Community MOs

- Report faxed to community oncologist with patient-specific trial listing (if mutation identified)
- Regular email summaries of patients enrolled and molecular profiling results
- Periodic newsletter with study updates
- Accessibility for rapid trial assessment when patients progress
COMPACT CLINIC

MOLECULAR PROFILING IN ADVANCED CANCER

What is Molecular Profiling?

There are differences in the DNA makeup of the cancer cells of each patient. Changes in the DNA makeup of cancer cells are known as mutations. Some cancers may respond to certain treatments better than others because of their mutations. Testing for mutations in cancer cells is known as molecular profiling.

Molecular profiling involves the additional testing of a stored sample of your cancer which was previously collected during a biopsy or surgery. Molecular profiling can only be done if your stored tumour sample contains sufficient amounts of tumour cells and DNA for testing.
COMPACT Accrual
(as of January 16, 2014)
COMPACT Metrics

- >300 referrals from 24 Ontario hospitals
- 258 patients enrolled
- 201 patients profiled and results reported
- 40% of patients with $\geq 1$ mutation(s)
- 18 patients matched to clinical trials
RELATIVE COST

# GENES COVERED

% OF HUMAN GENOME

= 1 HUMAN GENOME
3,000,000,000 BASE PAIRS
>22,000 GENES

SINGLE GENE SEQUENCING:
1 GENE
0.000075% OF GENOME

TARGETED SEQUENCING:
20–40 GENES
0.005% OF GENOME

MULTI–GENE SEQUENCING:
40–100 GENES
0.03% OF GENOME

WHOLE EXOME SEQUENCING:
>22,000 GENES
1% OF GENOME

WHOLE GENOME SEQUENCING:
>22,000 GENES
100% OF GENOME

courtesy Suzanne Kamel–Reid
Illumina MiSeq TruSeq Amplicon Cancer Panel

- Targeted sequencing of 48 genes and 212 amplicons (≥500x coverage)
- NextGENe v2.3.1 used for variant calling (5–10% threshold)
- Filter SNPs from 1000 Genomes and dbSNP

<table>
<thead>
<tr>
<th>Gene</th>
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<th>Gene</th>
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<tbody>
<tr>
<td>ABL1</td>
<td>ERBB4</td>
<td>JAK2</td>
<td>PIK3CA</td>
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<tr>
<td>AKT1</td>
<td>FBXW7</td>
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<td>ALK</td>
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<td>MLH1</td>
<td>SMARCB1</td>
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<td>CDKN2A</td>
<td>GNAQ</td>
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<td>CTNNB1</td>
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<td>EGFR</td>
<td>HRAS</td>
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<td>TP53</td>
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<tr>
<td>ERBB2</td>
<td>IDH1</td>
<td>PDGFRA</td>
<td>VHL</td>
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Comparison of Sequenom and MiSeq

<table>
<thead>
<tr>
<th></th>
<th>Sequenom (N=113)</th>
<th>MiSeq (N=113)</th>
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<tbody>
<tr>
<td>Number of Mutations</td>
<td>54</td>
<td>190</td>
</tr>
<tr>
<td>Patients with ≥ 1 Mutation (%)</td>
<td>49 (43%)</td>
<td>91 (81%)</td>
</tr>
<tr>
<td>Average # Mutations/Patient</td>
<td>0.48</td>
<td>1.68</td>
</tr>
<tr>
<td>Concordance for Detection of the Same Mutations</td>
<td>99.1%</td>
<td></td>
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</tbody>
</table>

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**Bar Chart:**

- Y-axis: # patients
- X-axis: # mutations/patient
- Yellow: Sequenom
- Blue: MiSeq

- 60 patients with 0 mutations
- 40 patients with 1 mutation
- 20 patients with 2 mutations
- 10 patients with 3 mutations
- 5 patients with 4 mutations
- 1 patient with 5 mutations
- 1 patient with 7 mutations
## Classification for NGS Reporting

### ACTIONABILITY*

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Recurrent Mutation in Gene</th>
<th>Non-Recurrent Mutation in Gene</th>
<th>Unknown</th>
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<tbody>
<tr>
<td></td>
<td>Same disease site</td>
<td>Different disease site</td>
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</tr>
<tr>
<td>1</td>
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<tr>
<td>5</td>
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*actionable = druggable/predictive/prognostic
Challenges of Clinical Characterization

- Data interpretation and reporting
- Tumor heterogeneity
- Return of incidental germline findings
- Algorithms for treatment matching
- Access to targeted drugs
- Infrastructure for clinical trials in rare cancer subpopulation
Molecular Basket Trial In Multiple Malignancies with Common Target Pathway Aberrances (MOBILITY–001)

MAPK or PI3K Pathway Alteration

PI3K + MEK inhibitors

Stage I

10 Ov/Gyn
10 NSCLC
10 Breast
10 Other*

Stage II

Expand if ≥1 response in each subgroup, stop if 0 response

9 Ov/Gyn
9 NSCLC
9 Breast
9 Other*

Stage III

7 Ov/Gyn
7 NSCLC
7 Breast
7 Other*

Deemed worthy of further interest if ≥5 responses in total in each subgroup

Overall study total = 40-104 patients

*includes non-gynae, NSCLC, breast, CRC, and melanoma tumors
Pancreas cancer and KRAS/NRAS mutant CRC

Stage I:
- 15 CRC
- 15 Pancreas
- Expand if ≥1 response in each subgroup, stop if 0 response

Stage II:
- 10 CRC
- 10 Pancreas
- Deemed worthy of further interest if ≥4 responses in total in each subgroup

Overall study total = 30-50 patients

MOBILITY-002
Cancer Genomics Projects at a Glance

- FFPE archived sample
- Fresh biopsy

22,000 genes (exome/genome)

# of genes

- IMPACT: 48 genes
- COMPACT: 23 genes
- MATCH

Multiple tumor types

Tumor type specific

- GENIUS
- REFLECT
- REACT
- HPV-SEQ
- NET-SEQ
CGP Subcommittees

1. Assay development
   - Chairs: Suzanne Kamel-Reid and Ken Adalpe

2. Bioinformatics
   - Chairs: Benjamin Haibe-Kaines and Michael Hoffman

3. Circulating DNA technology
   - Chairs: Trevor Pugh and Ming Tsao

4. Pharmacogenomics
   - Chairs: Geoff Liu and Tracy Stockley

5. Immunotherapy and sequencing; Patient-derived tumor xenografts
   - Chairs: Brad Wouters and Marcus Butler
Summary

• Genomic characterization can be integrated into the routine care of advanced cancer patients

• Some patients with refractory disease benefit from genotype–matched treatment

• New systems are needed to advance personalized cancer medicine
  – broader genomic characterization
  – access to genotype–matched trials
  – evaluation of clinical and cost effectiveness
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Golnar Rasty
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Nadia Amin
Celeste Yu
Amanda Giesler
Geeta Nathan
Helen Chow

Eitan Amir
David Warr
Ian Tannock
Srikala Sridhar
Christine Elser
Ronald Feld
Geoffrey Liu
Helen Mackay
Marcus Butler
Neesha Dhani
Monika Krzyzanowska
Jennifer Knox
Anthony Joshua
Anna-Marie Mulligan
Ilan Weinreb
Danny Ghazarian

Ontario

Princess Margaret Cancer Centre
The Princess Margaret Cancer Foundation • UHN
Division of Medical Oncology
Department of Medicine