Using TCGA data to inform on precision medicine in late-stage cancer settings

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**Personalized Oncogenomics**

- BC Cancer Agency – Cancer Care and Research
- Provincial population-based cancer control program
  - Prevention, Screening, Diagnosis and Treatment
- **Scope:**
  - POG aims to bridge divide between genomics research and clinical practice
  - identify tumour-specific therapeutic targets in cancer patients with late stage disease

**Consult & Consent**  ➔  **Specimens:**
- Tumour Biopsy
- Archival tumour
- Peripheral blood

**Libraries:**
- PCR-free genomes (T/N)
- FFPE genome
- Strand-specific RNA-seq

**Illumina Sequencing and Data Analysis**  ➔  **Therapeutic recommendation to Clinician**
Patients enrolled and data generated

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled since July 2012 (pediatric)</td>
<td>83 (8)</td>
</tr>
<tr>
<td>Biopsies performed</td>
<td>69</td>
</tr>
<tr>
<td>Tumour types</td>
<td>28</td>
</tr>
<tr>
<td>Metastasis tumour genome coverage</td>
<td>93x</td>
</tr>
<tr>
<td>Matched normal genome coverage</td>
<td>46x</td>
</tr>
<tr>
<td>Archival tumour genome coverage</td>
<td>46x</td>
</tr>
<tr>
<td>Average tumour RNA-seq reads</td>
<td>306M</td>
</tr>
<tr>
<td>Analysis reported (in progress)</td>
<td>50 (19)</td>
</tr>
<tr>
<td>Average time from biopsy to report</td>
<td>38 days</td>
</tr>
</tbody>
</table>

**Graph**: Bar chart showing the number of patients enrolled for each tumour type.
How POG guides treatment decision making

1) Providing directed cytotoxic chemotherapy choices & targeted therapeutic options
2) Complemented/corrected clinical tests
3) Changed diagnosis
4) Identifying primary tumour sites when previously unknown
1) Case POG 003 – SCC
Provided targeted therapeutic options

2007 2008 2009 2010 2011 2012 2013 2014

“red rash” on chest
Developed bleeding ulcerations
Diagnosed with Squamous cell carcinoma

Three lines of chemotherapy and multiple rounds of radiotherapy started in 2007

• Jan 2012 – new preauricular node
• Jun – Aug 2012 node and chest mass growing (pain and hearing loss)
• Sep 2012, preauricular and chest lesions biopsied for POG
POG 003: Squamous cell carcinoma of skin

**Single nucleotide mutations**
(truncating mutations)

- Chest: 2224 genes (134)
- Preauricular node: 4075 genes (222)
- 548 genes in common

**Small indels**
(frameshift mutations)

- Chest: 18 genes (13)
- Preauricular node: 22 genes (19)
- 17 genes
- 22 genes
POG 003 – Copy number variants

• Samples almost completely distinct
• Very few common breakpoints
DNA repair defects, PTEN loss, AKT1 gain
Therapeutic options, treatment and response

• Treatment:
  – High-level amplification and over-expression of *EGFR* in the **preauricular tumour** suggested **erlotinib**
  – PTEN homozygous loss and AKT gain and over-expression in the **chest** lesion suggested **everolimus**

• Response:
  – Dramatic reduction in the size and extent of his tumours
  – Hearing returned to his right ear
  – Dramatically reduced use of pain medications
  – After a few months, the pre-auricular tumour progressed, so we re-biopsied and sequenced this tumour

Dec 6, 2012

Jan 15, 2013
Progressed preauricular tumour

• Further *EGFR* amplification and over-expression observed
  – Higher copy number (55) than in the 2012 biopsy (32)
  – Highest expression level in all TCGA samples
2) Case POG 030 - NSCLC
Complemented/corrected clinical tests

• 68 yo male lifelong never smoker diagnosed with non-small-cell lung adenocarcinoma

Radiation and three lines of chemo between March and July 2013 but rapid progression

2013

Jan  Feb  Mar  Apr  May  Jun  Jul  Aug

Confirmed Non-small cell lung adenocarcinoma, metastasis in lymph node

FNA of right supraclavicular node - *EGFR* and *ALK* tests negative

Biopsied same node for POG
**EML4-ALK fusion found in this patient**

- Transcriptome and genome sequencing revealed chr2 inversion fusing *EML4-ALK* genes.

- Sequence analysis at chr2 breakpoints identified a further inversion and insertion into chr12 that appears to prevent Vysis dual-colour break-apart probe from hybridizing.

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**Diagram:**

- **EML4 exons 1-13**
  - coiled-coil domain
    - dimerization,
    - kinase activation

- **ALK exons 20-29**
  - tyrosine kinase domain

- FISH probes

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**chr2**

- inversion

**chr12**

- inversion & insertion into chr12
ALK and ROS1 are highly expressed in POG 030 (compared with TCGA lung adenocarcinoma and other POG lung cases)
Response to ALK inhibition (Crizotinib)

- **EML4-ALK** fusion, with high overall expression of **ALK** together with **ROS1** over-expression
- TKI Crizotinib was immediately administered
- The tumour responded dramatically

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Sept 4 2013 – before Crizotinib

Crizotinib started Sept 25
Scan from Dec 12, 2013
Evaluation of POG Results

• For each patient, sequenced ≥3 genomes (normal, archival, tumour) and 1 transcriptome (tumour)

• 82 consented patients with advanced cancer
  - 74 biopsies attempted
    - 3 biopsies failed, 2 patients withdrew consent
  - Full data available for 50 patients
    - 9 in progress, 6 on hold, 4 patients died during analysis phase
  - Clinically evaluated in 38 cases

• POG informative or actionable for treatment: 33/38 (87%)

• Treatment available and offered: 18/33 (55%)
  – ≥ 6 (18%) patients died during or shortly after analysis, precluding treatment
Personalized Oncogenomics - Phase II

- REB approval for 5,000 cases (in 5yrs)
- Move from ~1 pt / week to >1 pt / day
- Emphasis on genome + transcriptome sequencing
- Include the “oncopanel” for a rapid TAT “first look”
- Emphasis will expand beyond end stage patients
- Increase speed and accuracy of sequence analysis & report generation
- Verifying “actionable” results in clinical lab. prior to treatment
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