Impact of a Personalized Medicine Research Program (PMRP) Using Targeted Tumor Profiling and a Cloud-based Clinical Trials Matching Platform on Clinical Decision-making

Laboratory and Computational Tools to Enhance Clinical Decision Making
AACR Annual Meeting
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I have the following financial relationships to disclose:

Consultant for: GenomiCare Scientific Board Member, TBC Holdings, Inc.

Speaker’s Bureau for: Novartis Speakers’ Bureau

Employee of: Swedish Cancer Institute at Swedish Medical Center
Seattle, Washington

I will not discuss off label use and/or investigational use of specific agents in my presentation.
• Increasingly, genomic changes in patient’s tumors are used to inform individualized management.
• The optimal approach and impact of tumor profiling on cancer care remain important research questions.
• We report the impact on clinical decision-making by results from a Personalized Medicine Research Program in a research practice.
Challenges of Personalized Medicine

- Cost and access to genomic testing.
- Cost and access to indicated therapies.
- Lack of actionable gene alterations.
- Education of all stakeholders.
- Patient expectations.
- Complexity of interpretation of data.
- Access to big data solutions.
- Expansion of physicians’ comfort zone.
Swedish Cancer Institute (SCI)
Personalized Medicine Research Program (PMRP)

- **2014 Mar:** Personalized Medicine Program (PMP) Panel 1st Edition (68 gene panel).
- **2014 Sept:** SCI PMRP Protocol [Institutional Review Board (IRB) approved].
- **2015 Jan:** SCI Molecular Tumor Board.
- **2015 Nov:** Cloud-based PMRP IT Platform.
SCI PMRP: Methods

• A custom designed next generation sequencing (NGS) 68 gene alteration (GA) panel, covering clinically relevant genes and regions, was offered early in the course of management.
• GA were categorized as actionable (on label indication), or applicable [off label and/or clinical trial (CT) indication].
• The NGS results were used to:
  • Prioritize standard therapies;
  • Match patients (pts) with clinical trials (CT);
  • Serve as a data mining resource.
An IRB approved prospective registration protocol (PMRP) was activated in 2014, to establish a centralized longitudinal, molecular phenotypic, and research data repository.

- Primary endpoints include proportion of pts where NGS impacted management, to include CT enrollment, as determined by primary provider:
  - One time assessment provided at initial registration.

- A cloud-based informatics platform was developed to:
  - Manage PMRP;
  - Facilitate CT matching;
  - Perform quality assurance/quality improvement;
  - Pursue research initiatives.
SCI PMRP: Eligibility Criteria

Inclusion Criteria

- Pts with active malignancies or selected pre-malignant conditions.
- 18 years of age, or older.
- ECOG performance status of 0 to 2.
- A candidate for anti-cancer therapy.
- Life expectancy of at least three months.
- Measurable or evaluable disease is not required.
- Prior malignancy or multiple current malignancies allowed.
- Pts who previously had gene sequencing are allowed.
Exclusion Criteria

• Pts who are not able to understand and consent for themselves to the PMRP.
• Pts who do not have sufficient tissue available for the PMP Panel.
SCI PMRP: Recruitment /Enrollment

• **Enrollment:** 926 pts (as of March 12, 2017); initial focus on solid tumors.

• **Insurance Status:** No restrictions.

• **Cost to Participate in PMRP:** None (PMP Panel ordered by provider, and billed based on “medical necessity”).

• **Languages:** Consent form in English, Vietnamese, Korean, Japanese, Chinese (Mandarin & Cantonese), Russian and Spanish.
**SCI PMRP: Follow-up**

- Pts followed at least annually or with change of clinical status to:
  - Update genomic interpretation.
  - Update “on or off label” indications.
  - Update relevant clinical trials.
  - Consider repeat NGS testing.
- Provider and pt receive updated reports.
SCI PMP: Informatics Platform

Cloud-based Personalized Medicine Platform
Collect, manage, integrate, visualize, analyze & share

Molecular Pathology NGS Reports

External Labs
(e.g. TCGA - Human Genome Project)

Genomic Data & Tools

Synoptic Pathology

External Clinical Trials

Clinical Trials Management System

State/National Registries

Disease Site Registries (Research)

Providence / Swedish Enterprise Data Warehouse

Electronic Medical Records

Providence & Swedish Cancer Registries

Providence Research and Clinical Trials Website
(Public)

Clinical Interpretation
(e.g. annotation, therapeutic options, literature)

Existing Platforms
2017 – Platforms

Existing Interface
2017 – Interface

External Labs

State/National Registries

Disease Site Registries (Research)

Providence / Swedish Enterprise Data Warehouse

Electronic Medical Records

Providence & Swedish Cancer Registries

Providence Research and Clinical Trials Website
(Public)

Syncronic Pathology

External Clinical Trials

Clinical Trials Management System

Genomic Data & Tools

TCGA - Human Genome Project
SCI PMRP: Results

Demographics and Stage

• As of 03/12/2016, 926 pts gave informed consent, with 906 pts currently enrolled.
  • Median age 63.
  • 397 (44%) male; 509 (56%) female.
  • Of solid tumor pts with documentable stage: 132 pts (39%) had Stages I, II, or III; 203 pts had Stage IV (61%).
SCI PMRP: Results

Primary Disease Site

Most common documented primary sites

<table>
<thead>
<tr>
<th>Primary Site</th>
<th># of Pts</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>119</td>
<td>14%</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>115</td>
<td>14%</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>103</td>
<td>13%</td>
</tr>
<tr>
<td>Lung</td>
<td>93</td>
<td>11%</td>
</tr>
<tr>
<td>Ovary</td>
<td>49</td>
<td>6%</td>
</tr>
<tr>
<td>Hematologic Malignancies</td>
<td>46</td>
<td>6%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>39</td>
<td>5%</td>
</tr>
<tr>
<td>Uterus</td>
<td>29</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>26</td>
<td>3%</td>
</tr>
<tr>
<td>Skin</td>
<td>21</td>
<td>3%</td>
</tr>
<tr>
<td>Other Primary Site</td>
<td>21</td>
<td>3%</td>
</tr>
</tbody>
</table>
SCI PMRP: NGS Results

No NGS Results
87 (10%)

No GA
27 (3%)

GA
792 (87%)

Actionable / Applicable
591 (75%)

Unknown Significance
201 (25%)

# of Pts (%)
SCI PMRP: Top *Actionable* Gene Alterations (GAs)

<table>
<thead>
<tr>
<th>Gene</th>
<th># of GAs</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>132</td>
<td>63%</td>
</tr>
<tr>
<td>EGFR</td>
<td>20</td>
<td>10%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>17</td>
<td>8%</td>
</tr>
<tr>
<td>BRAF</td>
<td>15</td>
<td>7%</td>
</tr>
<tr>
<td>NRAS</td>
<td>11</td>
<td>5%</td>
</tr>
<tr>
<td>AKT1</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>TET2</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>PTEN</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>HRAS</td>
<td>2</td>
<td>1%</td>
</tr>
</tbody>
</table>
SCI PMRP: Top *Applicable* Gene Alterations (GAs)

<table>
<thead>
<tr>
<th>Gene</th>
<th># of GAs</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>242</td>
<td>28%</td>
</tr>
<tr>
<td>TPMT</td>
<td>86</td>
<td>10%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>82</td>
<td>9%</td>
</tr>
<tr>
<td>TYMS</td>
<td>78</td>
<td>9%</td>
</tr>
<tr>
<td>APC</td>
<td>67</td>
<td>8%</td>
</tr>
<tr>
<td>PTEN</td>
<td>54</td>
<td>6%</td>
</tr>
<tr>
<td>IDH1</td>
<td>34</td>
<td>4%</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>24</td>
<td>3%</td>
</tr>
<tr>
<td>TET2</td>
<td>23</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>22</td>
<td>3%</td>
</tr>
</tbody>
</table>
Did the NGS Test Results Impact Treatment Planning for the Patient?
Reported for 591 Pts with actionable/applicable GAs; 523 pts evaluable

Yes in 108 Pts (21%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Treatment (Tx)</td>
<td>33 (6%)</td>
</tr>
<tr>
<td>No Tx Given</td>
<td>19 (4%)</td>
</tr>
<tr>
<td>Tx Changed</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Tx Stopped</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Pts Enrolled onto CT</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

No in 415 Pts (79%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient Evidence</td>
<td>303 (58%)</td>
</tr>
<tr>
<td>Drugs/CT Access</td>
<td>99 (19%)</td>
</tr>
<tr>
<td>Refused Tx</td>
<td>17 (3%)</td>
</tr>
</tbody>
</table>
• Pts presented at Molecular Tumor Board appeared more likely to have NGS testing impact clinical decision-making (44% vs. 18%, p<.0001).
• Advanced stage pts appeared more likely to have NGS testing impact clinical decision-making (26% vs. 11%, p<.01).
• There appeared to be significant disease site differences with respect to the impact of NGS testing on clinical decision-making (p<.001); pts with colorectal cancers having the highest frequency of impact and pts with CNS cancers having the lowest frequency of impact.
Associations with Impact on Clinical Decision-Making (Cont’d)

• Pts with actionable (on-label) gene alterations appeared more likely to have NGS testing impact clinical decision-making than those with applicable (off-label or clinical trials) gene alterations (37% vs. 12%, p<.001).

• There appeared to be significant differences by gene alteration with respect to NGS testing impact on clinical decision-making (p<.001); BRAF and KRAS having the highest frequency of impact, and TP53, TMPT, and IDH1, having the lowest frequency of impact.
Conclusions

• NGS profiling of tumors with this 68 gene alteration panel has an impact on clinical decision-making in a minority, though substantial number of pts.
• Presentation at Molecular Tumor Board, advanced stage, and actionable gene alterations appeared to be associated with a higher frequency of impact on clinical decision-making.
• There appear to be differences in impact on clinical decision-making for pts across primary disease sites, as well as across gene alterations.
• The impact on clinical trial participation remains modest.
• Access to drugs and to clinical trials remains an important barrier.
Conclusions (Cont’d)

- “Insufficient evidence” accounted for the majority of cases in which clinicians described no impact on clinical decision-making.
- Increased use of Molecular Tumor Board may play an important role in increasing the clinical impact of NGS profiling of tumors.
- The IRB approved prospective registration protocol has been key to understanding the above.
- Exploration of larger prospective data sets will be important.