Biomarkers in clinical trials: Overview of roadmaps for PD/ prognostic/predictive biomarkers

Herbie Newell
Newcastle Cancer Centre
Northern Institute for Cancer Research
Targeted Therapies –
The Future of Cancer Treatment

Agents which exploit the molecular and cellular pathology of cancer:
– Oncogene antagonists
– Tumour suppressor gene agonists
– Immortality gene inhibitors
– Anti-angiogenic agents
– Anti-invasive and anti-metastatic drugs
Biomarkers – Definition

A biomarker is:

“A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or responses (pharmacologic or otherwise) to a therapeutic intervention”

Or

A test!
The Cancer “Journey”

1:3 of us will get cancer

– Am I going to get cancer?
– Have I got cancer?
– What kind of cancer is it?
– How bad is my cancer?
– What is the best treatment?
– Is the treatment working?
The Cancer Patient Journey

1:3 of us will get cancer
  – Am I going to get cancer? TESTS
  – Have I got cancer? TESTS
  – What kind of cancer is it? TESTS
  – How bad is my cancer? TESTS
  – What is the best treatment? TESTS
  – Is the treatment working? TESTS
Biomarkers in Cancer Management

Am I going to get cancer?

Predisposition biomarkers - Identification of individuals at risk of developing cancer
Biomarkers in Cancer Management

Have I got cancer?

Screening biomarkers - Early detection of cancer in the general or at risk populations
Biomarkers in Cancer Management

What kind of cancer is it?

Diagnostic biomarkers - Definition of tumour type, stage and grade
Biomarkers in Cancer Management

How bad is my cancer?

**Prognostic biomarkers** - Identification of the likely clinical disease course and hence appropriate therapeutic approach
Prognostic Biomarker-Driven Therapies for Medulloblastoma – Professor Steve Clifford

Disease biology:
Prognostic and predictive biomarkers

Individualised therapy

Favourable-risk: Therapeutic reduction
High-risk: Treatment intensification
Novel molecular agents: Stratification

Increased survival Reduced late-effects

Clinical trials
Validated medulloblastoma molecular and pathological prognostic biomarkers

- >300 published prognostication studies
- Markers showing consistent findings in ≥2 clinical trials cohorts

<table>
<thead>
<tr>
<th>Disease feature</th>
<th>Method of detection</th>
<th>Prevalence</th>
<th>Survival (risk-group vs. others)</th>
<th>Statistical analysis</th>
<th>Clinical trial</th>
<th>Cohort age range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Validated medulloblastoma molecular and pathological prognostic biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Validated medulloblastoma molecular and pathological prognostic biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wnt/Wg pathway activation (β-catenin nuclear stabilization)</td>
<td>IHC</td>
<td>27/109 (25%)</td>
<td>92% vs 85% (5 year OS)</td>
<td>p = 0.006 m</td>
<td>PNET3</td>
<td>3 - 16.8 yrs</td>
<td>Ellison et al., 2005</td>
</tr>
<tr>
<td>Desmoplasia (in infants ≤3 yrs)</td>
<td>Histopathological assessment</td>
<td>20/43 (47%)</td>
<td>85% vs 34% (7 year PFS)</td>
<td>p &lt; 0.001 m</td>
<td>HIT-SKK'92</td>
<td>&lt;3 yrs</td>
<td>Rutkowski et al., 2005</td>
</tr>
<tr>
<td>MYC gene amplification</td>
<td>FISH</td>
<td>5/84 (6%)</td>
<td>All dead at 5 yrs</td>
<td>p &lt; 0.001 m</td>
<td>PNET3</td>
<td>&gt;3 yrs</td>
<td>Lamont et al., 2004</td>
</tr>
<tr>
<td>MYC gene amplification</td>
<td>qPCR</td>
<td>5/111 (4.5%)</td>
<td>40% vs 66% (7 year OS)</td>
<td>NS</td>
<td>HIT '91</td>
<td>3 - 18 yrs</td>
<td>Rutkowski et al., 2007</td>
</tr>
<tr>
<td>Large-cell / anaplastic histology</td>
<td>Histopathological assessment</td>
<td>23/116 (20%)</td>
<td>57% vs -80% (5 year EFS)</td>
<td>p = 0.04 u</td>
<td>SJMB96</td>
<td>3.1 - 20.2 yrs</td>
<td>Geijer et al., 2006</td>
</tr>
<tr>
<td>Large-cell / anaplastic histology</td>
<td>Histopathological assessment</td>
<td>62/315 (17%)</td>
<td>~56% vs ~75% (5 year OS)</td>
<td>p = 0.024 m</td>
<td>PNET3</td>
<td>2.7 - 16.4 yrs</td>
<td>McManamy et al., 2007</td>
</tr>
</tbody>
</table>
Definition of Disease-Risk Stratification Groups in Childhood Medulloblastoma Using Combined Clinical, Pathologic, and Molecular Variables


- **WNT subgroup**
  - Favourable-risk (13%)
  - Standard-risk (60%)
  - High-risk (27%)

Progression-Free Survival (probability)

Time Since Start of Therapy (years)
The PNET5 MB and PNET6 MB Clinical Trials (2012-2018)

Surgery
Frozen tumour

Clinical staging
Molecular diagnostics and pathology review

Prospective biological studies

PNET5 MB
(5-10%)

PNET6 MB
(40%)

HIGH-RISK
(30%)

WNT

M+ MYC LCA

INTENSIFIED

STANDARD

REduced

First molecularly-driven trial in paediatric CNS tumours
Biomarkers in Cancer Management

What is the best treatment?

Predictive biomarkers - Patient enrichment to maximize likely benefit from specific therapies:
  - **Positive** – Patients with the biomarker should receive therapy
  - **Negative** – Patients with the biomarker should not receive therapy
Positive Predictive Biomarker
- *HER2* expression in breast cancer
Positive Predictive Biomarker
- HER2 amplification in breast cancer

Positive Predictive Biomarker
- Trastuzumab therapy in breast cancer

Most Active MAb: rhuMAb HER2
"Selective Targeting"

"Antagonize HER2" (rhuMAb HER2)

Breast Cancer Cell

p185^{HER2} receptors

"Antagonize HER2" (rhuMAb HER2)
Positive Predictive Biomarker  
- *HER2* amplification and trastuzumab therapy in breast cancer

<table>
<thead>
<tr>
<th>Study and <em>HER2</em> Amplification</th>
<th>No. of Assessable Patients</th>
<th>Objective Response (CR plus PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>H0649g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH positive</td>
<td>173</td>
<td>33</td>
</tr>
<tr>
<td>FISH negative</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>H0650g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH positive</td>
<td>82</td>
<td>28</td>
</tr>
<tr>
<td>FISH negative</td>
<td>29</td>
<td>1*</td>
</tr>
</tbody>
</table>
Negative Predictive Biomarker
- *K-Ras* and *B-Raf* Mutation in Colorectal Cancer

- **K-Ras** is mutated in 30-50% of colon cancer
- **B-Raf** is mutated ca. 10% of colorectal cancers
- Mutant *K-Ras* is a negative prognostic biomarker in colorectal cancer
Negative Predictive Biomarker
- *K-ras* mutation and EGFr-targeted antibody therapy in colorectal cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Size</th>
<th>WT <em>K-ras</em></th>
<th>Mut <em>K-ras</em></th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personeni</td>
<td>C +/- irinotecan</td>
<td>54</td>
<td>22%*</td>
<td>0%</td>
<td>0.05</td>
</tr>
<tr>
<td>Finocchiaro</td>
<td>C</td>
<td>81</td>
<td>27%</td>
<td>6%</td>
<td>0.02</td>
</tr>
<tr>
<td>De Rook</td>
<td>C +/- irinotecan</td>
<td>37</td>
<td>22%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Viret</td>
<td>C+irinotecan</td>
<td>32</td>
<td>22%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Stoehlmacher</td>
<td>C + irinotecan or +FOLFOX/FIRI</td>
<td>30</td>
<td>56%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Amado</td>
<td>Panitumumab</td>
<td>427</td>
<td>17%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Van Cutsem</td>
<td>C + FOLFIRI</td>
<td>540</td>
<td>59%</td>
<td>36%</td>
<td>-</td>
</tr>
<tr>
<td>Bokeneyer</td>
<td>C + FOLFOX</td>
<td>233</td>
<td>61%</td>
<td>33%</td>
<td>-</td>
</tr>
<tr>
<td>Tejpar</td>
<td>C + irinotecan</td>
<td>148</td>
<td>46%</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

C = Cetuximab, NS = not significant, ND = not determined, * % = response rate
Is the work focussed primarily on the discovery/development of a BM for application to clinical material?

Does the envisioned ultimate utility address an unmet clinical need?

Further basic research or sample access required, or redirect research elsewhere

Is there a sample collection for retrospective BM-clinical outcome correlation studies (BM Discovery – Stage 1/2)?

Do you have a BM assay?

Development of an accurate and reproducible assay to measure BM. Assay Development – Stage 1

Define BM distribution using the assay on specimens (~100) representative of the target patient population. Biomarker Discovery - Stage 1

Does the distribution of BM values indicate a BM with potential clinical utility?

Refinement of assay: Definition of SOPs and assay performance. Assay Development – Stage 2

Study the relationship between the BM and clinical outcome retrospectively. BM Discovery - Stage 2

Is there a correlation between the BM and clinical outcome?

Develop BM assay to GCLP standards. Assay Development – Stage 3

Validate the correlation between the BM and clinical outcome as a primary or secondary endpoint in a prospective study BM Qualification – Stage 1

Is the correlation between the BM and clinical outcome statistically robust?

Can the assay or clinical trial design be improved?

Undertake clinical trial where the BM defines randomization. BM Qualification - Stage 2

Is clinical outcome improved by prospective use of the BM?

Transfer BM to routine clinical practice

PROGNOSTIC/PREDICTIVE BIOMARKER (BM) ROADMAP
Clinically Established Predictive Biomarkers for Targeted Therapies

- **Positive Predictive Biomarkers**
  - *Her2/c-ErbB2* amplification: Trastizumab, lapatinib in breast cancer
  - *EGFr* mutation: Gefitinib, erlotinib in non-small cell lung cancer
  - *c-Kit* mutation: Imatinib in GIST
  - *Alk* amplification/translocation: Crizotinib in lymphoma/lung cancer
  - *B-Raf* mutation: Vemurafenib in melanoma
  - *Bcr-Abl* translocation: Imantinib, dasatinib, nilotinib in CML/ALL
  - Oestrogen receptor expression: Anti-oestrogens in breast cancer
  - *RAR* translocation: All-*trans*-retinoic acid in PML

- **Negative Predictive Biomarkers**
  - *K-Ras/B-Raf* mutation: Cetuximab, panitumumab in colorectal cancer
Biomarkers in Early Phase Trials with Targeted Therapies in Cancer

- **Predictive biomarkers**
  - Does the tumour have the target and is it functional?

- **Pharmacokinetic biomarkers**
  - Are active drug levels achieved?

- **Pharmacodynamic biomarkers**
  - Proof of mechanism (POM)
    - Does the drug hit its target?
  - Proof of concept (POC)
    - Is the required effect on tumour biology produced?

- **Surrogate response biomarkers**
  - Is the patient going to benefit?
Imatinib - POM PD Biomarker

Proof-of-mechanism (POM) pharmacodynamic biomarker - inhibition of CRKL phosphorylation
POC PD Assays for Apoptosis Induction by Targeted Agents

Courtesy of Professor Caroline Dive, Paterson Institute, Manchester
**PHARMACOLOGICAL BIOMARKER (BM) ROADMAP**

**Rationale**

- Does the envisioned ultimate utility address an unmet clinical need?
- Is the work focussed primarily on the discovery/development of the BM for application to clinical material?

**Development of an accurate and reproducible assay**

- Assay Development – Stage 1

- Establish a relationship between POM BM result and: i) dose, ii) plasma/tumour PK, iii) anti-tumour activity in animal models

**Biomarker Discovery and Assay Development**

- POM BM Discovery - Stage 1

**Assay Development**

- Use POM/POC assay in a small number of clinical samples to ensure assay feasibility

- Does the distribution of POM/POC BM values indicate an assay with clinical utility?

- Validate assay to GCLP

**Biomarker Qualification**

- Consider alternative doses or schedules

- Use BM data to inform compound development and clinical trial design
Biomarkers in Cancer Management

Is the treatment working?

Surrogate response biomarkers - Early prediction of ultimate clinical efficacy
18F-Fluorodeoxyglucose PET Scanning in GIST as a Surrogate Response Biomarker – Imatinib Therapy

PET Scans  Tumour
1 month apart

CT Scans
6 months apart
Biomarker Approaches

• Invasive
  – Tumour biopsy
  – Normal tissue biopsy
  – Blood borne

• Non-Invasive (Imaging)
  – MR
  – PET
  – Others (SPECT, ultrasound, etc)
Targeted Therapies and Stratified Medicine - Science fact NOT science fiction

- **Growth factor and receptor antagonists**
  - Bevacizumab, cetuximab, crizotinib, gefitinib, erlotinib, rituximab, sorafenib, sunitinib, trastuzumab

- **Second messenger or signal transduction inhibitors**
  - Imatinib, dasatinib, nilotinib, sorafenib, vemurafenib

- **Regulators of gene expression**
  - *All-trans* retinoic acid
  - SAHA
  - Anti-estrogens and anti-androgens
Predictive, Pharmacological and Surrogate Response Biomarkers for Stratified Medicine with Targeted Therapies in Cancer

Biomarkers
- Predictive
- PK
- PD – POM
- PD - POC
- Surrogate response