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

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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>Favourable risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wnt/Wg pathway activation</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>((\beta)-catenin nuclear stabilization)</td>
<td></td>
<td>10/69 (14%)</td>
<td>100% vs 60% (6 year EFS)</td>
<td>(p = 0.03^u)</td>
<td>SJMB96</td>
<td>3.1 - 20.2 yrs</td>
<td>Gejler et al., 2006</td>
</tr>
<tr>
<td>Desmoplasia (in infants ≤3 yrs)</td>
<td>Histopathological</td>
<td>20/43 (47%)</td>
<td>89% 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></td>
<td>assessment</td>
<td>17/28 (61%)</td>
<td>53% vs 17% (5 year OS)</td>
<td>NR</td>
<td>CNS9204</td>
<td>&lt;3 yrs</td>
<td>McMarnany et al., 2007</td>
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<tr>
<td><strong>Adverse risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<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></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</td>
<td>21/465 (4%)</td>
<td>(P &lt; 0.0001^U)</td>
<td>COG trials</td>
<td></td>
<td></td>
<td>Brown et al., 2000</td>
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<tr>
<td></td>
<td>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>Gejler et al., 2006</td>
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<tr>
<td></td>
<td></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>McMarnany et al., 2007</td>
</tr>
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</table>
Definition of Disease-Risk Stratification Groups in Childhood Medulloblastoma Using Combined Clinical, Pathologic, and Molecular Variables

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%)

WNT

PNET6 MB
(40%)

HIGH-RISK
(30%)

M+ MYC LCA

REduced

STANDARD

INTENSIFIED

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)
### Positive Predictive Biomarker

- **HER2 amplification and trastuzumab therapy in breast cancer**

<table>
<thead>
<tr>
<th>Study and HER2 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>
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<tr>
<td>FISH positive</td>
<td>173</td>
<td>33</td>
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<tr>
<td>FISH negative</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>H0650g</td>
<td></td>
<td></td>
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<tr>
<td>FISH positive</td>
<td>82</td>
<td>28</td>
</tr>
<tr>
<td>FISH negative</td>
<td>29</td>
<td>1*</td>
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</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*
PROGNOSTIC/PREDICTIVE BIOMARKER (BM) ROADMAP

Does the envisioned ultimate utility address an unmet clinical need?

Is the work focussed primarily on the discovery/development of a BM for application to clinical material?

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

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

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?

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

Rationale

BM Discovery and Assay Development

BM Qualification
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?
Mechanism of Action of Protein Kinases

**ATP**

**Protein Kinase**

**ADP**

**Protein Phosphatase**

**BIOLOGICAL RESPONSE**

**BIOLOGICAL RESPONSE**
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
Can POM/POC biomarker results equivalent to those that equal to anti-tumour activity in preclinical models be achieved at tolerated doses in patients?

**Biomarker Qualification**

Do you have a POC biomarker?

Investigate the relationship between POC BM and: (i) POM BM results (if available), (ii) dose, (iii) plasma/tumour PK and (iv) anti-tumour activity in animal models

POC BM Discovery – Stage 2

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

POM BM Discovery - Stage 1

Development of an accurate and reproducible assay

Assay Development – Stage 1

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

Assay Development - Stage 2

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

Validate assay to GCLP

Assay Development - Stage 3

Use POM/POC in Phase I/II clinical trials

Biomarker Discovery and Assay Development

Consider alternative doses or schedules

Biomarker Qualification

Use BM data to inform compound development and clinical trial design

Is the work focussed primarily on the discovery/development of the BM for application to clinical material?

Further basic research might be required

Does the envisioned ultimate utility address an unmet clinical need?

Rationale
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  
1 month apart

Tumour

Heart

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