Cancer Biomarkers: Hope, Hype or Help. Does the past predict the future?

ECMC Quality Assurance & Translational Science Network Group
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Definitions

- **Biomarker**: A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- **Clinical endpoint**: A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

- **Surrogate endpoint**: A biomarker intended to substitute for a clinical endpoint.

(NIH recommended definitions, 2001; Controlled Clinical Trials 22:485–502 (2001))
Types of Biomarkers

- **Risk/Predisposition biomarkers**: These identify individuals at increased risk of developing disease and can be identified in large population based studies, clinical trials or family studies, where examples include genetic screening for cancer pre-disposition genes such as BRCA1/2, APC or MLH1.

- **Screening biomarkers**: These aid in identifying disease at early stage and can be developed in large population based studies and/or clinical trials; an example being PSA for prostate cancer.

- **Diagnostic biomarkers**: These are used to define the presence of disease. They can be developed from large population based studies or from clinical trial data. Diagnostic biomarkers could also be used to detect recurrent disease after primary therapy. An example of this biomarker category is mammogram for breast cancer.

- **Prognostic biomarkers**: These indicate the likely course of the disease. Prognostic biomarkers can guide treatment decisions; i.e. cancer patients with prognostic biomarkers that predict a poor outcome could be selected for aggressive treatments to increase their chance of survival, whereas patients with biomarkers predicting a good outcome could be spared unnecessary treatments. For example, intensive combination adjuvant chemotherapy is appropriate for patients with extensive lymph node involvement – a poor prognostic biomarker - as opposed to lymph node negative breast cancer.

- **Predictive biomarkers**: These biomarkers identify subpopulations of patients who are most likely to respond to a given therapy. For example, breast cancer patients with oestrogen receptor positive tumours are more likely to respond to anti-endocrine therapies, and only patients with HER2 amplification should be given trastuzumab (Herceptin) therapy.

- **Pharmacological biomarkers**: These measure the effects of a drug treatment on a specific target. Such pharmacodynamic biomarkers can only be fully interpreted with the corresponding pharmacokinetic data.
Pharmacodynamic Biomarkers: The ho(y)pe

<table>
<thead>
<tr>
<th>Question</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does it hit the target in man?</td>
<td><strong>Proof of mechanism (PoM)</strong> e.g. enzyme inhibition, receptor blockade</td>
</tr>
<tr>
<td>Does it have an effect on the disease phenotype?</td>
<td><strong>Proof of Principle (PoP)</strong> e.g. Increased cell death markers (apoptotic markers- eg. TuNeL),</td>
</tr>
<tr>
<td>Does this result in a beneficial clinical effect?</td>
<td><strong>Proof of Concept (PoC)</strong> e.g. Tumour size reduction,</td>
</tr>
</tbody>
</table>
Pharmacodynamic Biomarkers: Helping decision making

- Delineate in man potentially "biologically active" exposures of an investigative agent with the aim of defining "minimally biologically effective doses" (MBED). This is to more accurately estimate the lower dose range for Phase II testing;
- Provide data to support the selection of an optimal dosing schedule;
- Make more scientifically based "no go" development decisions if either no biological activity in tumor can be delineated at MTD; or the margin between MBED and MTD in the context of variable pharmacokinetics is considered challenging.

**Question to FDA & EMEA:**

Do you agree that conceptually pharmacodynamic biomarkers offer utility to drug development decisions with respect to:

- making go/no go decisions
- defining MBED
- guiding optimal schedule

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Go/No Go: Losing a loser
(AZD5438; 2005)

Maximum Tolerated Single dose
In volunteers

Maximum Tolerated Repeat dose
In patients

Convincing biological activity

Pre-dose
Post-dose

Go/No Go: Picking a winner
(AZD6244; 2005)

Response

Drug target - \( \text{pERK} \)

Tumour growth - \( \text{Ki67 proliferation} \)

Stable Disease

Pre-dose

Post-dose

Progression

B. Vose: Analyst Briefing 2006
A. Adjei: NCI-EORTC-AACR 2006
Dose response - AZD1152

% Change in M30

Day of Therapy

Dose response:
- 100mg
- 200mg
- 300mg
- 450mg

AstraZeneca
Dose and Duration: Cedirinib

Tumour blood flow & permeability – DCE-MRI

Baseline 2 days 28 days 56 days

Structural imaging – MRI
Baseline 28 days 56 days


AstraZeneca
Schedule: AZD3409

Once daily insufficient coverage of target

Twice daily sufficient coverage of target

Drove decision to alter clinical schedule

Note: 24 h placebo data combined from cohorts 1-3 only

Wilson, EORTC-NCI-AACR; October 2004
Business model to “qualify” a biomarker in Oncology

Identify potential biomarker(s) (3y prior to clinic)

A. Assay development in human tumour and/or non-tumour tissue (Feasibility Study)

B. Variability in intended tumour and/or non-tumour tissue (Reproducibility Study)

C. Preclinical sensitivity testing with Candidate Drug (Positive control/PK-PD)

D. Clinical sensitivity / positive control study in man IF possible

Biomarker with clinical utility
Set Go/No Go Hurdles
AZD5438: cyclin dependent kinase (CDK) inhibitor

Tumour cell apoptosis inducer with no effect on normal resting cells

- CD nomination to first human dose in 5 months
- Proof of mechanism in healthy volunteers within 12 months of nomination
  - AZD5438 inhibits the Phosphorylation of pRb in tissues at well tolerated doses
- Now in patient trials

Brent Vose: AstraZeneca Annual Business Review
October 2004
Identify Potential Biomarker

Key:  
- No commercially available antibody defined
- cdk4/2
- cdk4
- cdk2

Diagram showing E2F, N, and C domains with numbered positions and colored circles indicating potential biomarkers for cdk4/2, cdk4, and cdk2.
Feasibility

3 mm biopsy punch under local anaesthesia

Actual biopsy

Well tolerated

9/10 subjects said that they would undergo repeat biopsies

No adverse events on any real note
Human Buccal Tissue: Feasibility and Reproducibility results

<table>
<thead>
<tr>
<th></th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Between Subject</td>
</tr>
<tr>
<td>phospho-pRB</td>
<td>19.0</td>
</tr>
<tr>
<td>pRB</td>
<td>13.7</td>
</tr>
<tr>
<td>pRB ratio</td>
<td>10.6</td>
</tr>
<tr>
<td>phospho-p27</td>
<td>15.9</td>
</tr>
<tr>
<td>p27</td>
<td>17.8</td>
</tr>
<tr>
<td>p27 ratio</td>
<td>23.9</td>
</tr>
</tbody>
</table>

Time in hours

No. positive cells per mm of basement membrane

- p27
- p-pRB
- pRB
- p-p27
In vivo xenograft

Pre-dose

Post-dose
Setting your hurdle

Competitor data

Your own pre-clin data

Effect on p-Rb Phosphorylation
in SW620 Tumours

Human variability

CV% = 11%

E7070 (AS) S795

Pre-80%  Post-5%

AstraZeneca
Now your ready to use it in anger….and if nothing happens make a kill decision with confidence
A reminder on terminology

Biomarkers

- **Predictive markers**
  - Determines likelihood of response to therapy

- **Response after receiving therapy**
  - **PD biomarkers**
    - Changing in response to therapy

- **Measured prior to therapy**
Amongst patients treated with drug, biomarker +ve patients do better than biomarker –ve patients.
but the same is true for patients treated with control, biomarker +ve patients do better than biomarker –ve patients.
biomarker+ve patients treated with drug do better than biomarker +ve patients treated with control
PFS by Mutation Status
– Overlaid KM Curves

Randomised treatment
- Gefitinib EGFR M+
- Gefitinib EGFR M-
- Carboplatin / paclitaxel M+
- Carboplatin / paclitaxel M-

Probability of progression-free survival vs Time from randomisation (months)
PM Trials are smaller and quicker…

…or are they?
Assume you had a drug which doubled the time to progression (HR=0.5) in biomarker +ve subjects and no effect in biomarker –ve subjects and the target for the drug is only present in 25% of people.

1. Unselected Design

```
All subjects -> Drug
          |          |
          |          | Control
```

2. Prospective selection

```
All subjects -> All tested
          |          |
          |          | +ve pts
          |          | -ve pts
          |          | Drug
          |          | Control
```
No effect in –ve patients

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>E</th>
<th>Effect (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve (25%)</td>
<td>6 mo</td>
<td>12 mo</td>
<td>0.50</td>
</tr>
<tr>
<td>–ve (75%)</td>
<td>6 mo</td>
<td>6 mo</td>
<td>1.00</td>
</tr>
<tr>
<td>All patients</td>
<td>6 mo</td>
<td>7.5 mo</td>
<td>0.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N req’d to enter$^1$</th>
<th>N req’d to screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Prospective selection</td>
<td>117</td>
<td>468</td>
</tr>
</tbody>
</table>

$^1$median follow-up of 18 months assumed
...but this assumes...
A. the selection test is perfect...
B. biomarker –ve patients have no effect

What happens to the numbers if this isn’t the case
An imperfect test lessens the advantage of a targeted trial

<table>
<thead>
<tr>
<th>Sens, Spec</th>
<th>PPV</th>
<th>C</th>
<th>E</th>
<th>Effect size</th>
<th>N req’d to enter</th>
<th>N req’d to screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%,100%</td>
<td>100%</td>
<td>6 mo</td>
<td>12 mo</td>
<td>0.50</td>
<td>117</td>
<td>468</td>
</tr>
<tr>
<td>95%, 75%</td>
<td>56%</td>
<td>6 mo</td>
<td>9.4 mo</td>
<td>0.64</td>
<td>260</td>
<td>613</td>
</tr>
<tr>
<td>75%, 95%</td>
<td>83%</td>
<td>6 mo</td>
<td>11 mo</td>
<td>0.55</td>
<td>149</td>
<td>663</td>
</tr>
<tr>
<td>75%, 75%</td>
<td>50%</td>
<td>6 mo</td>
<td>9 mo</td>
<td>0.68</td>
<td>317</td>
<td>845</td>
</tr>
</tbody>
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Remember: An Unselected trial required 1000 patients
Anyway, assume we have the perfect test, what happens if there is some modest (~1/3 of biomarker +ve) effect in –ve pts?

Is a selected design still best?
Even a small effect in –ve pts erodes the apparent advantage of a targeted trial

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<td>–ve (75%)</td>
<td>6 mo</td>
<td>7.5 mo</td>
<td>0.80*</td>
</tr>
<tr>
<td>All patients</td>
<td>6 mo</td>
<td>8.7 mo</td>
<td>0.69</td>
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<tbody>
<tr>
<td>All patients</td>
<td>384</td>
<td></td>
</tr>
<tr>
<td>+ve (25%)</td>
<td>117</td>
<td>468</td>
</tr>
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* Effect in –ve pts = 1/3 effect in +ve patients)
In a PM strategy we would need to be very confident that (i) we had a very good test and (ii) the untargeted population achieved no benefit from treatment in order to gain clinical trial efficiency in conducting the trial in only biomarker +ve subjects.
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