Evaluation of relationship between biomarker and selected clinical endpoints in oncology

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Biostatistician 2, Clinical Services - Global Delivery Network

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Bullet points

• *Biomarkers – Introduction*

• *Biomarker included study designs*

• *Methodology*

• *Case study – rRNA to GAPDH ratio as Biomarker*
Biomarkers – Introduction

Biomarkers

“... a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”

In simple, a naturally occurred molecule or gene for identification of a disease or a pathological process.

This includes: Diagnostic tests, imaging technologies and any other objective measures of patient’s health status.
Biomarkers – Introduction (cont....)

Why Biomarkers?

*They become more important for three reasons:

- Measure the effectiveness of new drugs on relevant Biomarkers
- Pressure for new, promising drugs to be approved for marketing as rapidly as possible – rely on Biomarkers
- Corresponding need for early detection of safety signals

Biomarkers clinical end points directly measure how a patient feels, functions, or survives
Biomarkers – Introduction (cont....)

Majorly include

• Biochemical markers
• Cellular markers
• Cytokines
• Genetic markers
• Gene expression profiles
• Imaging markers
• Physiological markers
• Other patient or tumor measurements
Biomarkers – Introduction (cont....)

Biomarkers are already in common use in patient management and used for following:

• Early detection
• Diagnosis
• Treatment selection

Examples:
• Prostate-specific antigen (PSA) is used to monitor progression of disease in prostate cancer,
• Carcinoembryonic antigen (CEA) in colorectal cancer
• .....
Biomarkers – Introduction (cont.….)

Categorized

• Prognostic biomarkers, which affect the outcome of patients in terms of a clinical end point.

• Predictive biomarkers, which affect the effect of a specific treatment on a clinical end point.

• Surrogate biomarkers, which may replace a clinical end point in clinical trials carried out to evaluate the effect of a specific treatment.
Biomarkers – Introduction (cont.…)

Associations

• **Individual level association**
  - Between the biomarker and clinical end point

• **Trial level association**
  - Between the effects of the treatment and the biomarker
Biomarkers – Introduction (cont.….)

Associations

Treatment effects could be,
• log odds ratios for binary end points
• log hazard ratios (HR) for time-to-events

The bubble size is proportional to the number of patients in each trial.
Biomarker included study designs

Randomized design for intermediate risk:
Low risk require only standard therapy,
High risk require experimental therapy,
Intermediate risk are randomized to either standard or experimental treatment.

Stratified randomized design:
Patients stratified to Biomarker status
And then randomized to either standard or experimental treatment.

Reference: Kevin Kelly, Susan Halabi (2010). Oncology Clinical trials, Demos Medical Publishing
**Biomarker included study designs (cont....)**

**Biomarker-based strategy design:**
Randomly assigned to have their treatment determined by their biomarker status or to receive standard treatment.

**Modified biomarker-based strategy design:**
Randomly assigned to have their treatment determined by their biomarker status or to be randomized again to either standard or experimental treatment.

Reference: Kevin Kelly, Susan Halabi (2010). Oncology Clinical trials, Demos Medical Publishing
### Biomarker included study designs (cont....)

#### Minimum Requirements For Statistical Validation

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Feature</th>
<th>Study design</th>
<th>Approx.. Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic</td>
<td>Biomarker predicts clinical outcome</td>
<td>Case-control or Cohort study</td>
<td>&gt; 100 patients</td>
</tr>
<tr>
<td>Predictive</td>
<td>Biomarker predicts treatment effect on clinical outcome</td>
<td>Large randomized trial</td>
<td>&gt; 500 patients</td>
</tr>
<tr>
<td>Surrogate</td>
<td>Treatment effect on biomarker predicts treatment effect on clinical outcome</td>
<td>Several randomized trials, or a large trial on with several units of analysis</td>
<td>&gt; 10 units of analysis &gt; 1,000 patients</td>
</tr>
</tbody>
</table>

Reference: Kevin Kelly, Susan Halabi (2010). Oncology Clinical trials, Demos Medical Publishing
Methodology

A prognostic biomarker can be considered for clinical interest only, if its impact on the clinical end point of interest is large enough, hence the number of patients required will often be smaller than that required to establish or confirm a treatment benefit.
Methodology (cont....)

“For a prognostic biomarker, the baseline value of the biomarker, or changes in the biomarker over time, should be correlated with the clinical end point in untreated or in treated patients.”

“Establish statistically,, No study design required”
Case study

Considering a trial approached in this context:

For a Phase 1 Study to identify the Maximum Tolerated dose (MTD) of the combination of study treatment and carboplatin administered by intravenous infusion every three weeks. This is a dose escalation study with 3+3 design, and the recommended dose considered from the previous research and the dose escalation of both study treatment and carboplatin will be escalated until the desired dose level is reached or until 2 or more DLTs are observed in dose cohort.
Case study (cont....)

**Primary endpoints:**
- To determine the MTD of the combination of study treatment and carboplatin
- Safety adverse events will be evaluated
- Pharmacokinetic evaluations

**Secondary endpoints:**
- Best response
- Overall response
- Tumor response
- To investigate the relationship between the selected biomarkers and efficacy and safety outcomes.

*Approx. 55 patients, suggested to enroll in the study.*
**Case study (cont.)**

**Trial design:**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Course 1</th>
<th>Course x</th>
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<tbody>
<tr>
<td></td>
<td>14 days prior to Day 1 of course 1</td>
<td>Day 02</td>
<td>Day 02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 08 (± 3 days)</td>
<td>Day 08 (± 3 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 15 (± 3 days)</td>
<td>Day 15 (± 3 days)</td>
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</tbody>
</table>
### Case study (cont....)

### Tables reference for endpoints

#### Summary of duration of stable disease

<table>
<thead>
<tr>
<th>Response Duration (days) *</th>
<th>Starting Dose (mg/m²/dose)/(mg/m²/course)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.80/2.80</td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
</tr>
<tr>
<td>Mean</td>
<td>XX.X</td>
</tr>
<tr>
<td>SD</td>
<td>XX.XX</td>
</tr>
<tr>
<td>Minimum</td>
<td>XX</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
</tr>
<tr>
<td>Maximum</td>
<td>XX</td>
</tr>
</tbody>
</table>
Case study (cont....)

**Duration of overall response**

<table>
<thead>
<tr>
<th>Response Duration (days)*</th>
<th>2.00/2.00</th>
<th>3.50/3.50</th>
<th>4.00/4.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean</td>
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<td>XX.X</td>
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<tr>
<td>SD</td>
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<tr>
<td>Minimum</td>
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<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Maximum</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
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</table>

*Summary of Duration of Overall Response All Patients*
### Case study (cont....)

### Summary of Tumor Response

<table>
<thead>
<tr>
<th>Best Tumor Response</th>
<th>2.80/2.80</th>
<th>3.50/3.50</th>
<th>4.36/4.38</th>
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</thead>
<tbody>
<tr>
<td>CR</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>PR</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>SD</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>PD</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>
Case study (cont....)

A selected housekeeping genes ribosomal ribonucleic acid \((rRNA)\) and \(Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) ratio\) was utilized as a biomarker in evaluating a relationship between the biomarker and selected efficacy, safety outcomes.

\(rRNA\) is a nucleic acid that together with proteins makes up the ribosome.

\(GAPDH\) is a multifunction enzyme (for energy metabolism)
Case study (cont.….)

Percentage change from baseline in the biomarker (rRNA/GAPDH ratio) and maximum percentage shrinkage from baseline in the target tumor regions presented in a two dimensional scatter plots and Spearman’s coefficient of correlation calculated

Percentage change from baseline in the biomarker (rRNA/GAPDH ratio) and percentage change from baseline in neutrophil counts, during the first course for selected visits presented in a two dimensional scatter plots and Spearman’s coefficient of correlation calculated
Case study (cont....)

Scatter Plot of Percentage change in Biomarker and Maximum Percentage tumor shrinkage from Baseline

Spearman’s Rank Correlation Coefficient to assess the relationship between percentage change in biomarker and maximum percentage tumor shrinkage from baseline.
Case study (cont....)

Scatter Plot of Percentage change in Biomarker and Percentage change in Neutrophil count from baseline to Course 1-day8

Spearman’s Rank Correlation coefficient to assess the relationship between percentage change in biomarker and percentage change in neutrophil count from baseline.
Case study (cont....)

Scatter Plot of Percentage change in Biomarker and Percentage change in Neutrophil count from baseline to Course 1-day15

Spearman’s Rank Correlation coefficient to assess the relationship between percentage change in biomarker and percentage change in neutrophil count from baseline.
Conclusion

• The results doesn’t show a better effect (no correlation) when correlating with the selected endpoints.

• The sample chosen for the study were (may) not tested for their basic biomarker evaluations.
Points to take

• Road to Implementing Biomarkers is steep

• Each selected biomarker must be rigorously evaluated before consideration
QUESTIONS ?
THANK YOU
FOR YOUR ATTENTION