Evaluation of relationship between biomarker and selected clinical endpoints in oncology

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IF YOU REPEAT LIES OFTEN ENOUGH YOU CAN DO STATISTICS

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
<u>how a patient feels, functions, or survives</u>

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***

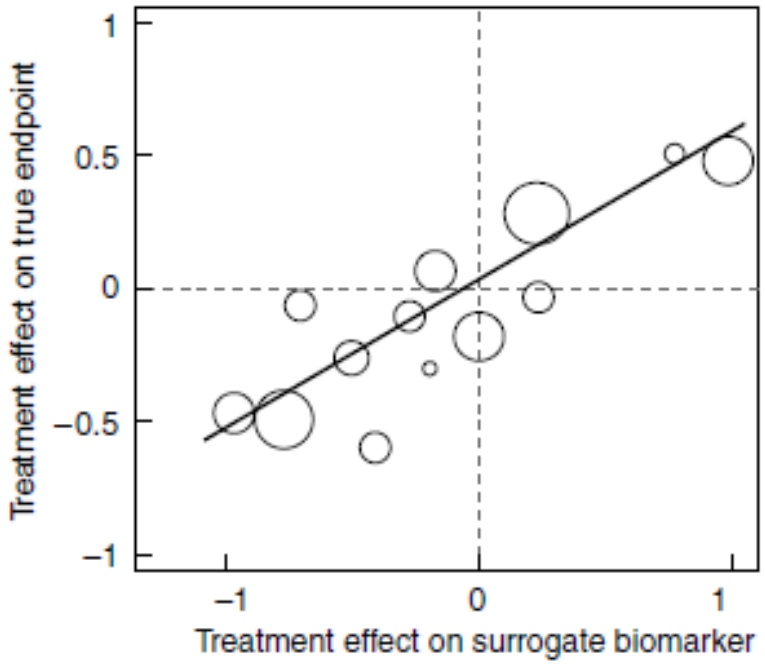
  - Between the effects of the treatment and the biomarker

Biomarkers – Introduction (cont.…)

Associations

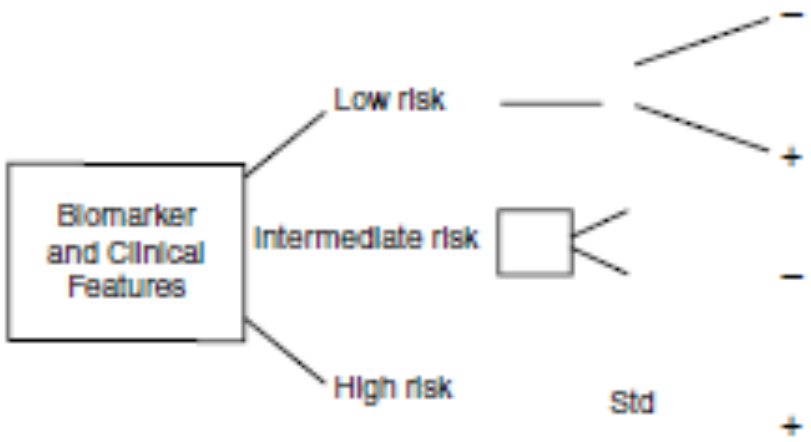
Treatment effects could be,

- 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

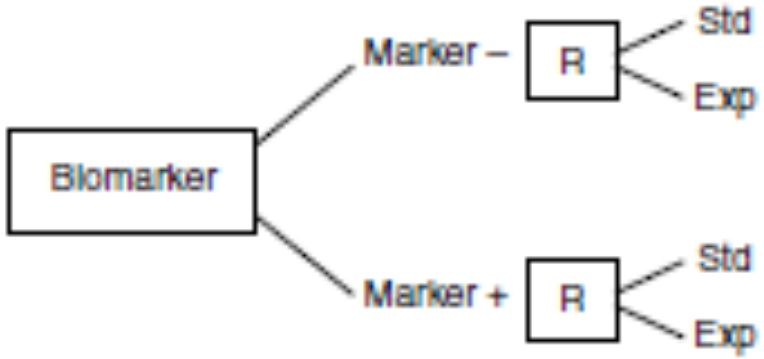


Randomized design for intermediate risk:

Low risk require only standard therapy,

High risk require experimental therapy,

Intermediate risk are randomized to either standard or experimental treatment.



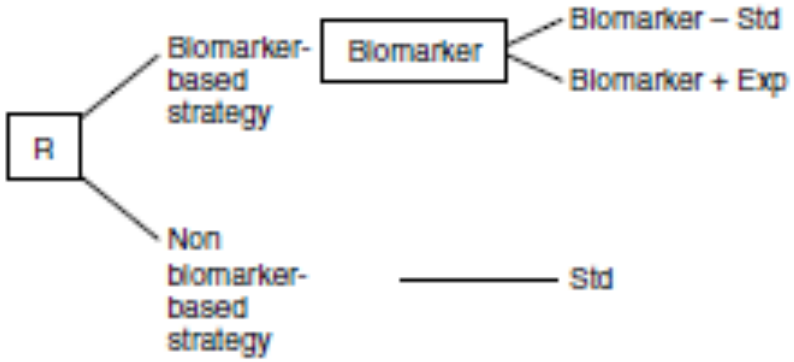
Stratified randomized design:

Patients stratified to Biomarker status

And then randomized to either standard or experimental treatment.

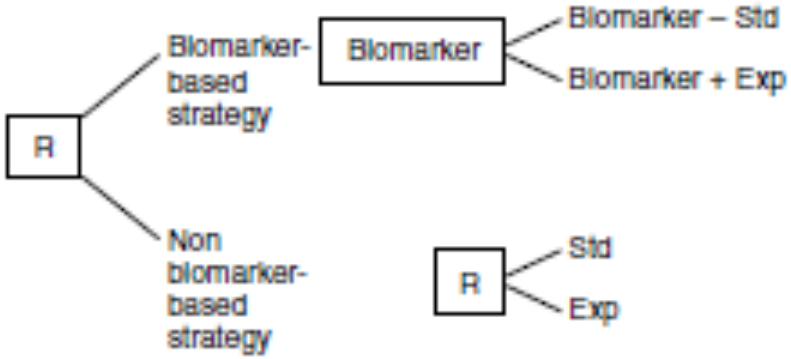
Reference : Kevin Kelly , Susan Halabi (2010). Oncology Clinical trials , Demos Medical Publishing

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

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:

	Baseline	14 days prior to Day1 of course 1
	Course 1	Day 02
		Day 08 (± 3 days)
		Day 15 (± 3 days)
	Course x	Day 02
		Day 08 (± 3 days)
		Day 15 (± 3 days)

Case study (cont.…)

Tables reference for endpoints

Summary of duration of stable disease

Summary of Duration of Stable Disease
All Patients

Response Duration (days)*	Starting Dose@ (mg/m2/dose)/(mg/m2/course)		
	2.80/2.80	3.50/3.50	4.38/4.38
N	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx
Median	xx.x	xx.x	xx.x
Maximum	xx	xx	xx

Case study (cont.…)

Duration of overall response

Summary of Duration of Overall Response
All Patients

Response Duration (days)*	Starting Dose@ (mg/m2/dose)/(mg/m2/course)		
	2.80/2.80	3.50/3.50	4.38/4.38
N	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx
Median	xx.x	xx.x	xx.x
Maximum	xx	xx	xx

Case study (cont.…)

Summary of Tumor Response

Summary of Tumor Response
All Patients

Best Tumor Response*	Starting Dose@ (mg/m2/dose)/(mg/m2/course) 2.80/2.80	3.50/3.50	4.38/4.38
CR	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PR	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SD	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PD	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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.

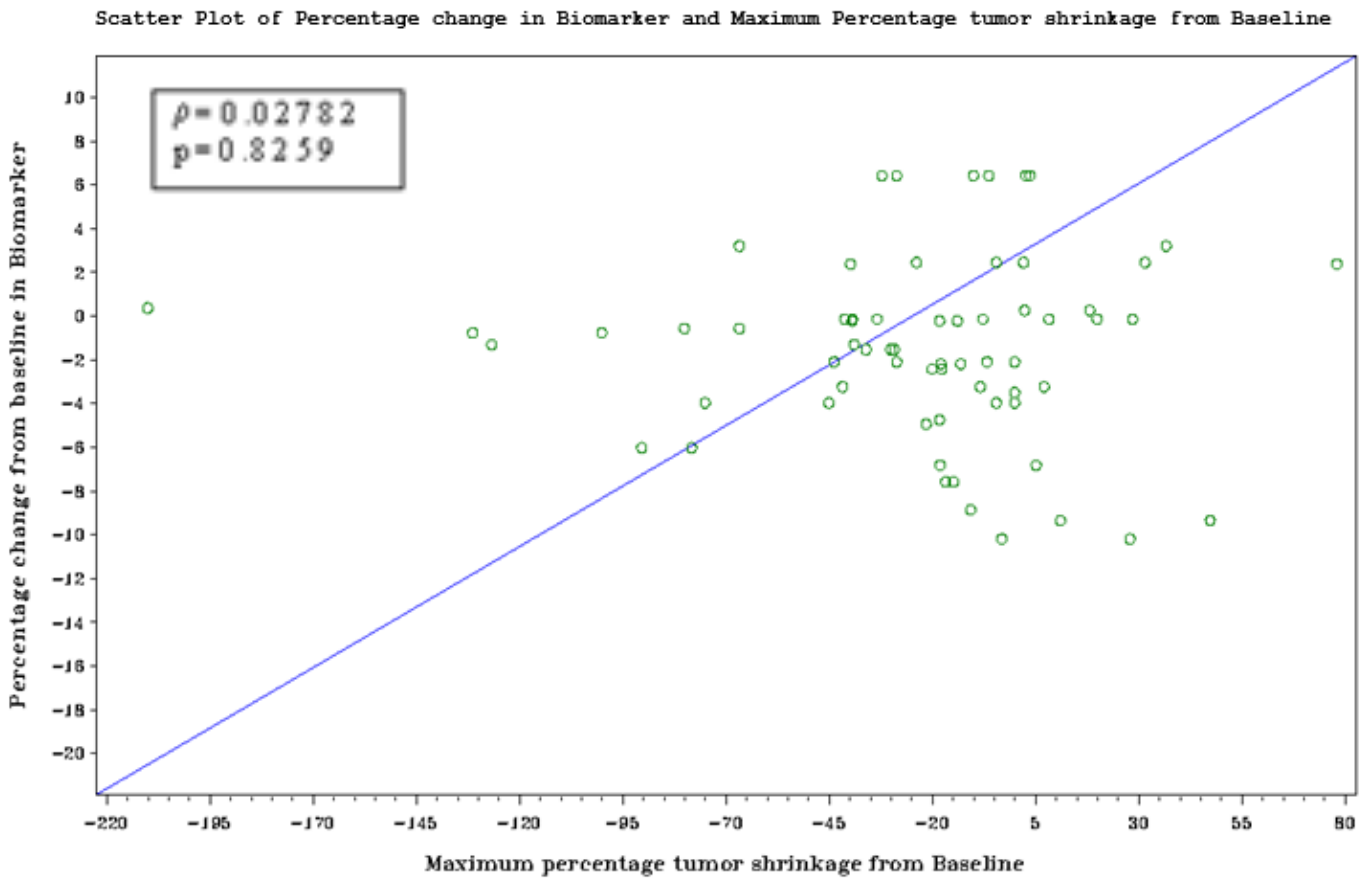
GAPDH is a multifunction enzyme (for energy metabolism)

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

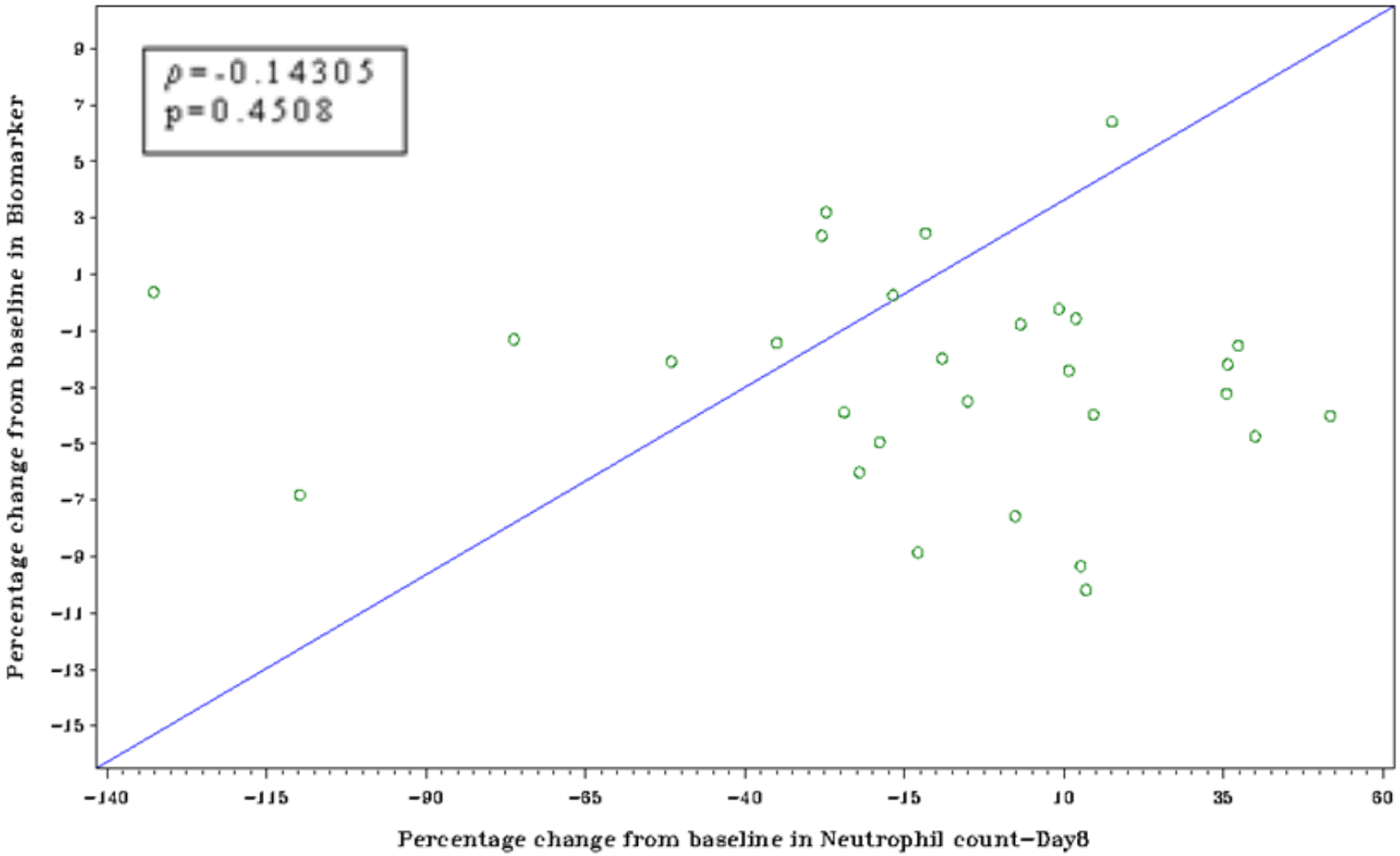
Case study (cont.…)



Spearman's Rank Correlation Coefficient to assess the relationship between percentage change in biomarker and maximum percentage tumor shrinkage from baseline.

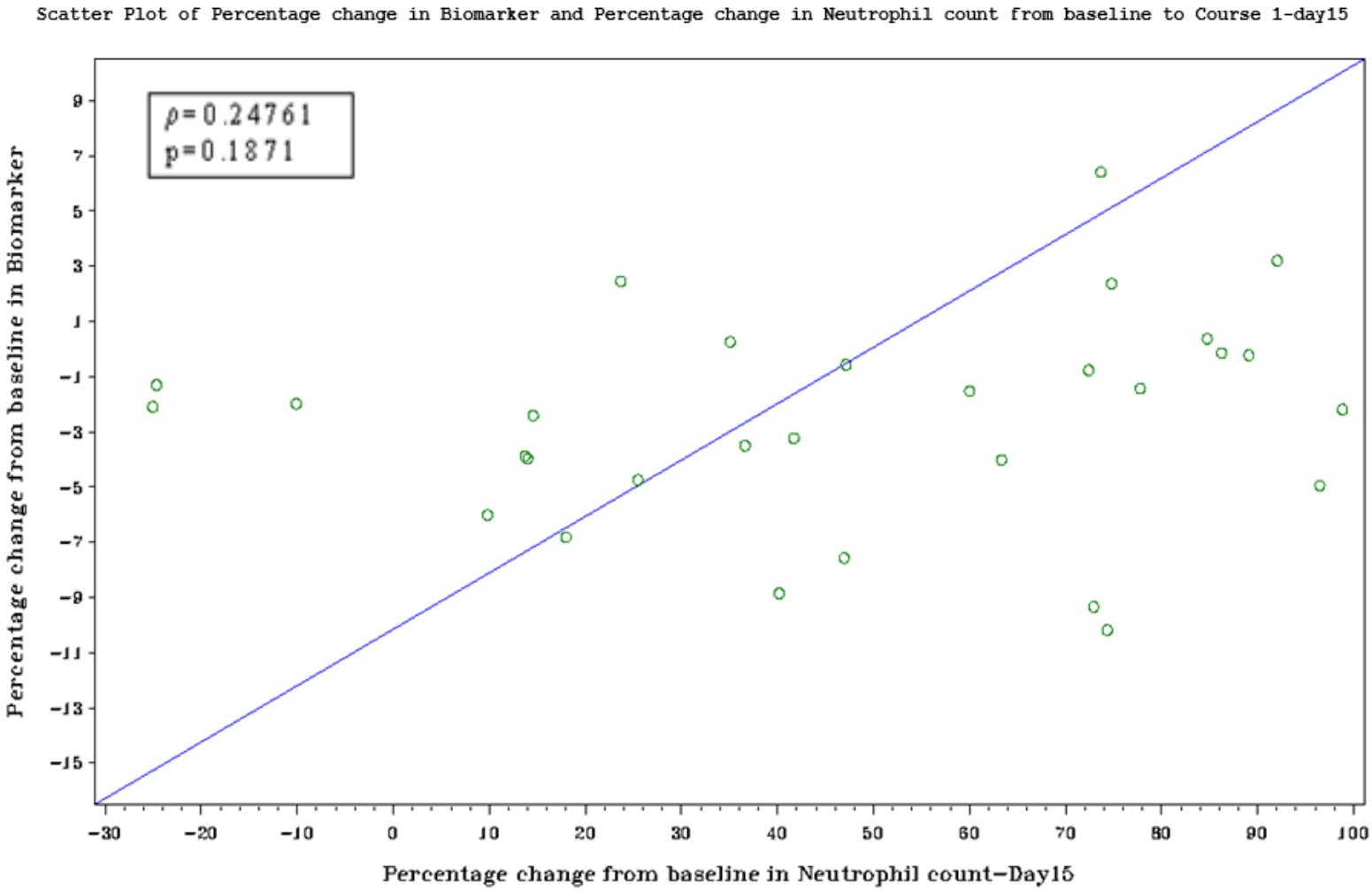
Case study (cont.…)

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.…)



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