Summary Report

Survival Analysis Results of Clinical Trial on Biomarker and Treatment Effects on Event of Interest

Introduction of the problem: Investigating the effect of a new biomarker on the risk of an event and the effect of treatment on the event in a completed clinical trial

Research hypotheses: A) Higher biomarker values indicate an increased rate of the event of interest, B) Lower biomarker values can identify which participants will benefit more from treatment

Outcome : The outcome of interest in this study is the occurrence of the event (STATUS = 1).

- *Survival time defined as the variable "DAYS" , which is the number of days from the participant's baseline visit to the last visit before the event occurred or the end of the study.*
- *Censoring occurs when the event of interest has not occurred by the end of the study or when a participant is lost to follow-up.. The "LAST_DATE" variable used to identify the last visit for each participant, and a "1" in the "STATUS" variable at the last visit indicates that the participant had the event of interest.*

Method: Cox proportional hazards model, controlling for other covariates

Main findings:

- The Cox proportional hazards model suggests that the biomarker and treatment have significant effects on the risk of the event of interest, and the effect of treatment depends on the level of the biomarker.
- The model supports the research hypotheses that higher biomarker values indicate an increased rate of the event of interest and that lower biomarker values can identify which participants will benefit more from treatment.
- Higher biomarker values indicate a 2.14 times higher hazard of experiencing the event of interest.
- Treatment SOC+ADT leads to a 2.3 times higher hazard of experiencing the event compared to other treatments.
- Treatment effect depends on the level of the biomarker
- The treatment SOC+ADT is effective for participants with low biomarker levels but not for those with high biomarker levels.

Conclusion: Hypotheses A and B are supported by the analysis results

The Cox PH models assesses the effect of the biomarker and treatment on the hazard of experiencing the event of interest, controlling for other covariates in the dataset. Total 6 Models are compared. Overall, Model 3 seems to provide the best fit, as it includes the most significant predictors and the interaction term, which suggests that the effect of biomarker on survival depends on the treatment received.

The coefficients of the model suggest:

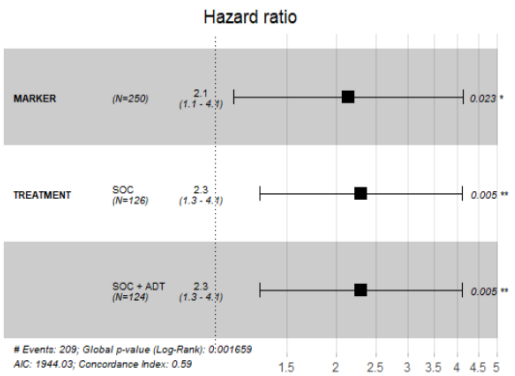
- For the biomarker variable, a one-unit increase in the biomarker value is associated with a hazard ratio of exp(0.7604) = 2.1391 (p-value=0.0234). This means that participants with higher biomarker values have a 2.14 times higher hazard of experiencing the event of interest compared to those with lower biomarker values, adjusting for the other covariates in the model.
- For the treatment variable, participants receiving SOC+ADT treatment have a HR 2.3[95% CI 1.3-4.1] times higher hazard of experiencing the event compared to those receiving a different treatment (p-value=0.0049).
- The interaction term between biomarker and treatment suggests that the effect of treatment on the hazard of experiencing the event depends on the level of the biomarker (p-value=0.0002). Specifically, the hazard ratio for the treatment SOC+ADT compared to the other treatment is 0.1587 for participants with low biomarker levels, indicating that the treatment reduces the hazard by 84%, while for participants with high biomarker levels the hazard ratio is greater than 1, indicating that the treatment is not effective for them.

Based on these results, we can conclude:

- **Hypothesis A is supported by the model results.** Higher biomarker values indicate an increased rate of the event of interest, even after controlling for other covariates in the model.
- **Hypothesis B is also supported by the model results.** The interaction term between biomarker and treatment suggests that the effect of the treatment on the hazard of experiencing the event depends on the level of the biomarker. Specifically, the treatment SOC+ADT is effective for participants with low biomarker levels but not for those with high biomarker levels.

Characteristic	HR[1]	95% CI[1]	p-value
MARKER	2.14	1.11, 4.13	0.023
TREATMENT			
SOC	—	—	
SOC + ADT	2.30	1.29, 4.10	0.005
MARKER * TREATMENT			
MARKER * SOC + ADT	0.16	0.06, 0.42	<0.001

[1] HR = Hazard Ratio, CI = Confidence Interval



To answer the questions Q1 to Q5

To answer the following questions regarding the data set

1. **Explore the data and report on any potential data issues.**
   - Exploratory Data Analysis are conducted to check for missing or inconsistent data and outliers, as well as to examine the distribution of the biomarker and clinical covariates.
     - ***CLIN_COV2 has value 2500 outlier, so we replaced using mean.***
     - ID number: P15 P125 has multiple records, which raises a data quality issue. P15 has 2 records with different baseline dates and follow-up visit data not being the same.P125 has 3 records which could be a real occurrence of the participant having the event of interest twice with a long time gap between the two events. 2 patients ID number: P22 P141 ,their STATUS not coupled with the corresponding VISIT.ID number P198, VISIT 4 and VISIT 5 recorded as "failed".
     - To address this issue, the investigator should: Review the data carefully and investigate whether the two records for P15 are accurate. Contact the study site to obtain additional information about the participant's medical history to confirm whether they had experienced the event of interest twice for participant P125.If the two records are accurate, the investigator should decide whether to exclude one of the records.

2. **Provide a basic "Table 1"**

Characteristic	**Overall**, N = 250[1]	**SOC**, N = 126[1]	**SOC + ADT**, N = 124[1]	**p-value**[2]
MARKER	0.53 (0.30)	0.54 (0.30)	0.52 (0.30)	0.6
CLIN_COV1				0.3
pT1-2a	81 (32%)	39 (31%)	42 (34%)	
pT2b-3a	87 (35%)	40 (32%)	47 (38%)	
pT3b+	82 (33%)	47 (37%)	35 (28%)	
CLIN_COV2	9.8 (5.9)	9.3 (6.2)	10.2 (5.6)	0.3

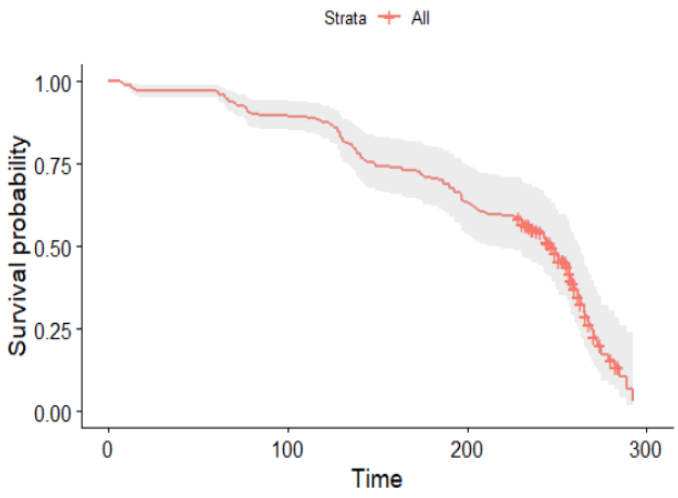
[1] Mean (SD); n (%)

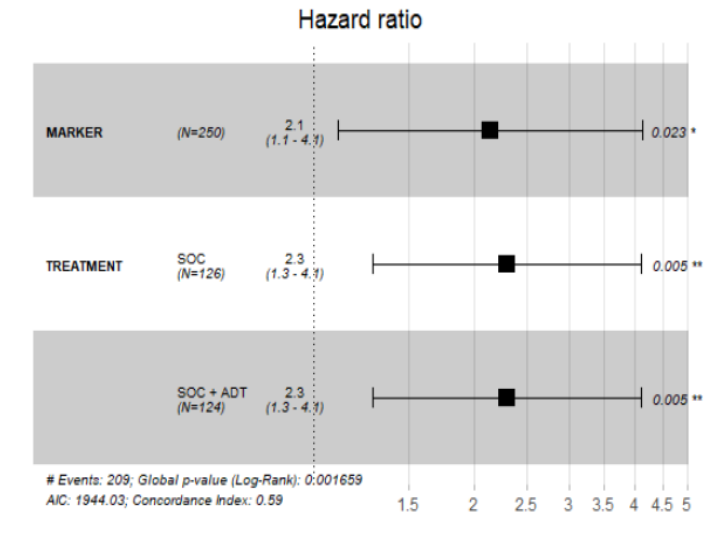
[2] Wilcoxon rank sum test; Pearson's Chi-squared test

To answer the following questions regarding the data set

3. **Fit and briefly interpret Cox PH models to address the investigators hypotheses. Provide a rough visualization to aid in the interpretation of all models.**

    - This visualization can help to confirm the main findings of the study and provide an intuitive way to interpret the results.





3. **All models are included in a submitted manuscript. Reviewer #1 asks, verbatim, "Please adjust to account for multiple comparisons". What would be your suggestion to the investigator in response?**

    - My suggestion is: When conducting multiple tests, it is important to adjust for the increased risk of type 1 errors (false positives) due to chance alone. One common method for controlling the family-wise error rate (FWER) is the Bonferroni correction.

4. **The investigator later discloses that CLIN_COV2 is also measured at each visit and sends you this additional information. Would you utilize this information? Why or why not, and how would you do it?**

    - Yes. if CLIN_COV2 is a potential confounder or effect modifier, it should be included in the analysis to improve the accuracy of the estimates, and it should be added as a covariate or interaction term in the Cox proportional hazards model accordingly.

Appendix R code (attached PDF)