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An Efficient R Shiny App for E-R Analysis in Oncology Drug Development

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ABSTRACT

Analysis of the Exposure–response (E-R) relationship is an approach that is extensively utilized to support dose selection and optimization by characterizing the relationship between drug concentrations, efficacy and safety. It's one of critical component in the submission package to seek regulatory approval for the oncology product.

With consideration of the importance of the E-R analysis, a BDS structure ADaM dataset (ADER) has been generated and a related R Shiny app has been developed in Dizal for efficient support multi-disciplinary internal review, decision-making, validation of vendor's reports and future E-R report generation.

The main features of R Shiny app include:

1. Dynamically show the plots/tables of EDA (Safety Endpoints and Efficacy Endpoints).
2. Dynamically perform the covariate selection for final model building.
3. Create the specific plots needed in the E-R report.

INTRODUCTION

While contemporary drug development in oncology strives to deliver novel therapies to Participants rapidly, it is also important to optimize dosing regimens to improve patient-centered care. Doses selected for pivotal trials may be efficacious doses, but not necessarily optimal to minimizing toxicity and maximizing clinical efficacy for all participants.

Exposure–response (E-R) analysis is an approach that is used to support dose selection by characterizing the relationship between drug concentrations and efficacy/safety endpoints. A variety of E-R analyses have supported dose labelling of many approved oncology drugs.

Based on the importance of E-R analysis in the process of drug development, we want to develop an interactive tool that can facilitate the use of various departments of clinical development, to provide them quickly and conveniently with information.

R Shiny is all about reactivity. It's a paradigm that allows you to build responsive and interactive applications by implementing data-driven interfaces. Changes triggered by the user will be immediately reflected in the application. That is the reason why we build our E-R platform on R shiny.

This paper will describe the process of analysis method, analysis dataset (ADER) construction and the E-R analysis and reports R Shiny app in detail.

E-R ANALYSIS PLAN

In this paper, we would employ one of the ongoing E-R analysis plan along with a dummy E-R dataset used.

E-R ANALYSIS DATASET CONSTRUCTION

The construction of final ADER dataset needs ADSL, ADPPK, safety datasets (e.g. ADAE, ADLB, ADVS, etc.) and efficacy datasets (e.g. ADRS, ADTTE, etc.) and baseline datasets (e.g. ADBASE, etc.) as input datasets.

You can create ADER study by study and then combine all the study or you can also create ISS and ISE datasets and then create ADER.

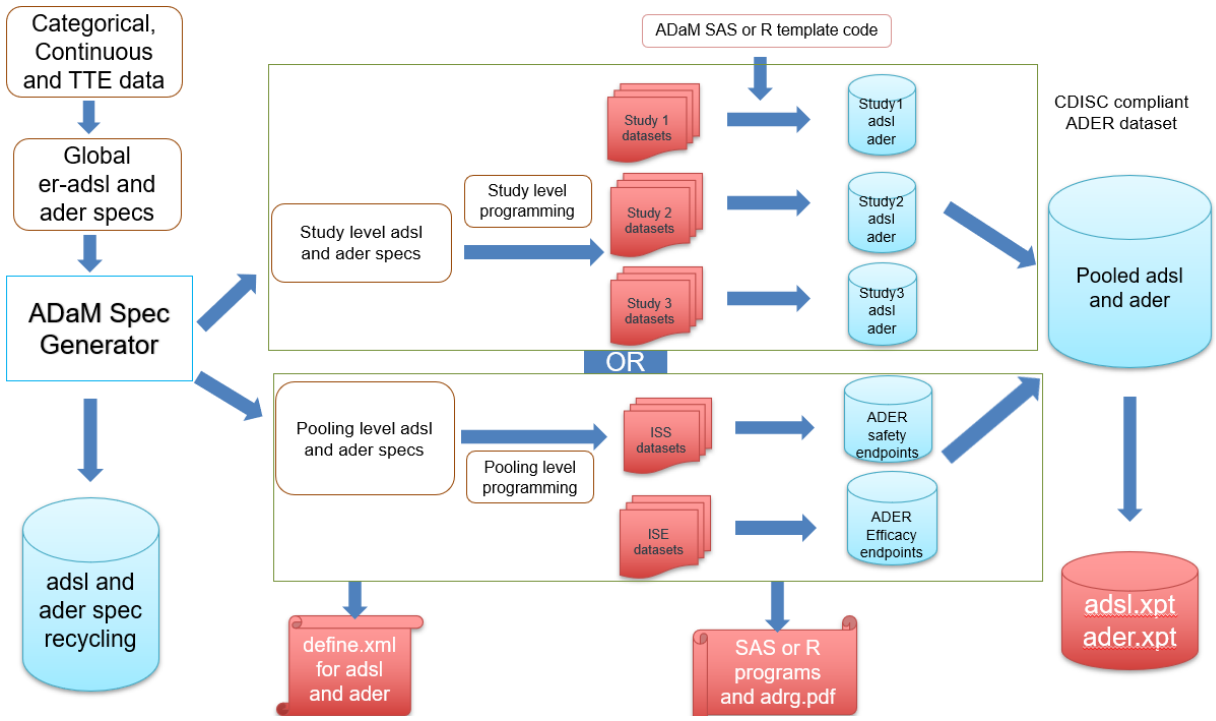


Figure 1. Workflow of ADER dataset construction

Safety and Efficacy Population

The E-R analysis dataset will pool safety event data collected in all treated participants from all patient studies (Study A, B, C, D) as well as efficacy outcome from participants who received at least 1 dose of study compound from Study B. Participants will be defined as evaluable for the E-R analyses if they have both PK and relevant efficacy or safety data available. The population flags are listed in Table 1.

Population Flag	Label	Participants
SAFFL	Safety Analysis Flag	All participants 4 Studies
EFF01FL	Efficacy Analysis Flag 01	Specific Participants in Study B

Table 1. Study population in ADER dataset

Safety and Efficacy Endpoints

You can find the safety and efficacy endpoints and the model types we use for the final models and study scopes respectively from Table 2 below:

Study (PROJID)	**Endpoints Type (PARCAT1)**	**Data/models type (PARCAT2)**	**Endpoints (PARAM/PARAMCD/PARAMN)**
Study B	Efficacy	Binary/logistic regression model	Objective Response Rate (ORR), defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR)
Study B	Efficacy	Continuous model	Best change from baseline in tumor size (sum of longest diameters in target lesions)
Study B	Efficacy	Time to event/cox proportional hazard model	Duration of response (DoR), defined as the time from the first documented response to radiographic disease progression or death due to any cause (whichever occurs first), in the subset of participants with confirmed CR or PR
Study B	Efficacy	Time to event/cox proportional hazard model	Progression Free Survival (PFS), defined as the time from the first dose of study compound to the first documentation of radiographic disease progression or death due to any cause, whichever occurs first
All 4 Studies	Safety	Binary/logistic regression model	Grade ≥3 TEAE Serious TEAE Any Grade and Grade 3 or worse: – Diarrhea – Rash (grouped terms): Rash, Rash maculo-papular, Dermatitis acneiform, Acne, Dermatitis, Papule, Rash macular, Rash popular, Rash pruritic – Anemia (grouped terms): Anemia, Iron deficiency anemia, Normocytic anemia – CPK increased – … TEAE leading to dose reduction TEAE leading to dose modification (drug interruption or dose reduction)

Table 2. Summary table of Endpoints and Model types

Exposure Metrics

Safety and efficacy reported for individual participants will be merged with individual study compound exposures predicted by the final population PK model. The analysis dataset will include following metrics in Table 3:

Metrics Main Type	Metrics Subtype (Variables in ADER)	Label
First Dose Exposure Metrics	CMAXSSFD	Max Conc. at Steady State by First Dose
	CMINSSFD	Min Conc. at Steady State by First Dose
	AUC24SFD	24h AUC at Steady State by First Dose
Mean Dose Exposure Metrics	CMAXSSMD	Max Conc. at Steady State by Mean Dose
	CMINSSMD	Min Conc. at Steady State by Mean Dose
	AUC24SMD	24h AUC at Steady State by Mean Dose
Mean Exposure Metrics	CMAXME	Max Conc. by Mean Exposure
	CMINME	Min Conc. by Mean Exposure
	AUC24ME	24h AUC by Mean Exposure

Table 3. Summary table of Exposure Metrics

The difference of definition of Mean Dose Exposure and Mean Exposure is listed below.

Mean Dose Exposure: Dosage information up to the onset of each Efficacy/Safety endpoints (Mean Dose = Total Dose / Total Dose time, then use the PopPK model to get predicted exposure metrics like $AUC_{24,ss}$, $C_{max,ss}$, $C_{min,ss}$, etc.)

Mean Exposure: Use PopPK model directly get exposure metrics derived from concentration data of each day up to the onset of Efficacy/Safety and then calculate mean exposure metrics.

The exposure metrics will be derived for each patient based on available dosing information and parameter values predicted by the final population PK model and will account for dose modifications and interruptions during treatment with study compound.

Covariates

Table 4 includes the covariates in ADER datasets for model building.

Variables	Label	Covariates Type
BRMETASN	Brain Metastatic Tumor	Categorical
WTBL	Baseline Body Weight (kg)	Continuous
ECOG	ECOG Status	Categorical
SMOKE	Smoke Status	Categorical
POLYM	Polymorphism	Categorical
SUMDIABL	Baseline Sum of Diameter of Target	Continuous

	Tumor (mm)	
REGION1	Geographic Region 1	Categorical
REGION1N	Geographic Region 1 (N)	Continuous
AGE	Age	Continuous
SEX	Sex	Categorical
SEXN	Sex (N)	Continuous
RACE	Race	Categorical
RACEN	Race (N)	Continuous
ETHNIC	Ethnicity	Categorical
ETHNICN	Ethnicity (N)	Continuous
TRT01A	Planned Arm Code	Categorical

Table 4. Summary Table of Covariates

Other Information

Variables in table 5 are basic information of studies and used to derive information above.

Variables	Label	Comment
USUBJID	Unique Subject Identifier	
USUBJIDN	Unique Subject Identifier (N)	
TRTSDT	Date of First Exposure to Treatment	Use for Derive Mean Dose and Mean Exposure Metrics
ADT	Analysis Date	
EXDUR	Duration after first dose (days)	
FAMT	First Amount of Dose Received (ug)	
MAMT	Mean Amount of Dose Received (ug)	
CNSR	Censor	For KM Plots and Cox PH Models
EVNTDESC	Event or Censoring Description	
ATOXGRN	Analysis Toxicity Grade (N)	CTCAE Grade

Table 5. The Summary Table of Other Information

EXPLORATORY DATA ANALYSIS (EDA)

Individual exposures will be visualized by box-whisker plots across binary and dichotomized continuous data. A tabular summary of binary and continuous efficacy and safety responses will be provided by exposure quartiles and dose group. The exploratory analysis for time-to-event efficacy endpoints will consist of Kaplan-Meier plots stratified by exposure quartiles and by dose group.

STATISITCAL MODEL METHODOLOGY

Binary Endpoints

Binary endpoints will be analyzed by logistic regression models based on the following equation:

$$log\left(\frac{p_i}{1-p_i}\right) = Intercept + Slope \times Exposure_i + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}$$

p_i is the probability of response (or AE for safety variables) for participant *i*, Intercept is the logit of the probability of response in the absence of study compound, Slope is the slope of the relationship between exposure and the logit of the probability of response, Exposure_i is the predicted exposure for participant *i*, $\beta_1 \ldots \beta_p$ is the vector of parameters for covariate effects, and $X_{i1} \ldots X_{ip}$ is the vector of covariate variables for participant *i*.

Continuous Endpoints

For continuous endpoints, similar methodology will be used based on the equation below:

$$Continuous\ response = Intercept + Slope \times Exposure_i + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}$$

Time-to-Event (TTE) Endpoints

Cox proportional hazard (PH) models will be developed to describe the time-to-event responses. The basic form of the Cox PH TTE model is shown below. The first equation relates the probability of being event-free up to time *t*, *S(t)*, to the hazard function *h(t)*:

$$S(t) = e^{-\int_0^t h(\tau)d\tau}$$

The hazard function is modeled according to the equation below:

$$h(t) = h_0(t) \times f(\text{Exposure}_i, \beta_X) \times \exp\{\beta_{v_1}(v_1) + \cdots + \beta_{v_n}(v_n)\}$$

$h_0(t)$ is a non-parametric baseline hazard. The general function, *f*, represents the effect of individual exposure as a predictor of the event and β_X, the coefficient for the effect of the predictor. $v_1, \ldots v_n$ are potential or known risk factors (covariates), and the coefficients (β) the corresponding log-hazard ratios.

Covariate evaluation

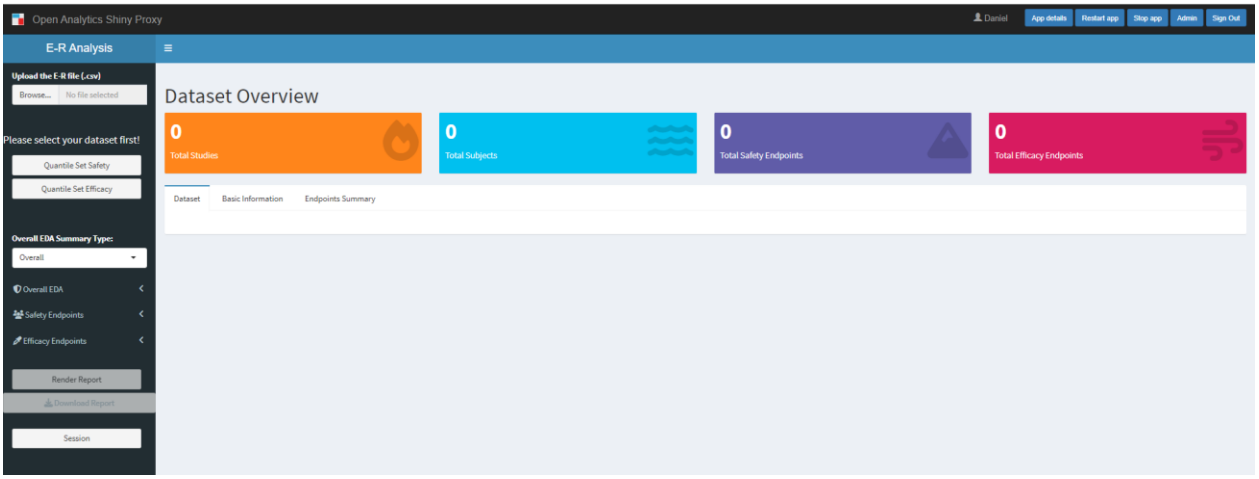
In E-R analyses where exposure is identified as a statistically significant predictor of response (at P=0.05), additional covariate analysis will be performed.

Initially, a full model with all the interested covariates will be constructed. Subsequently, a stepwise covariate model (SCM) building strategy will be performed with the parameter-covariate relationships. Variance Inflation Factor (VIF) check will be performed to detect whether multicollinearity exists in a regression model. Forest plots will be used to check covariates influence in the final models.

E-R R SHINY APP

According to the above analysis plan, we create a shiny app to meet the analytical needs. We use shinyproxy (version 3.0.2) to deploy our app packaged into a docker image for easily paralleled-accessed by multiple users.

Display 1 is the main interface when you log in your app.



Display 1. Former Main Interface for E-R Platform

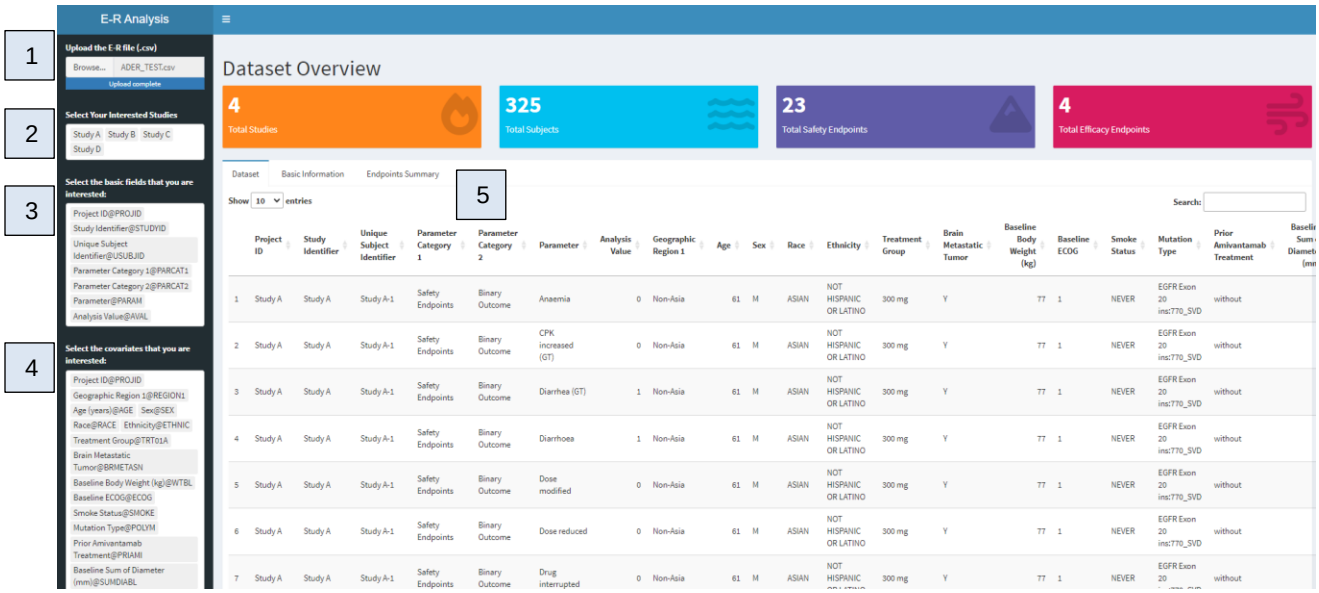
DATASET IMPORT AND DATASET OVERVIEW

Once you prepare your ADER dataset (For now this app only supports csv file), you can upload your dataset onto the platform (part 1), and you will get the dataset overview interface like Display 2.

The 2, 3, 4 parts are designed as multiple selection drop down list which you can add or remove studies, basic information (i.e., study information, subject ID, endpoints information, exposure information and other supplementary information) and covariates.

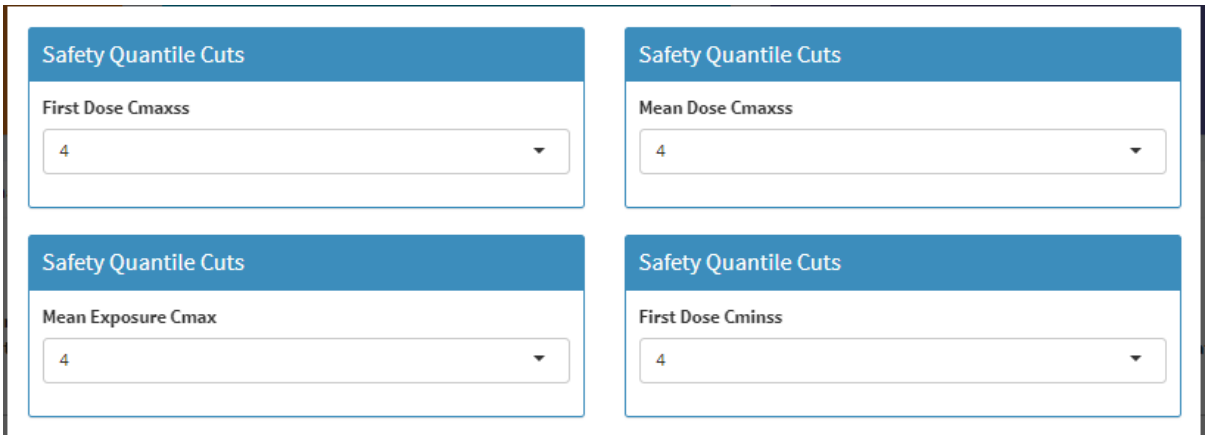
Part 5 is main panel for dynamically displaying the information you selected from 2, 3, 4 parts.

You can check dataset, basic information (summary of variables) and Endpoints summary from this part.



Display 2. Dataset Overview Interface

'Quantile Set Safety' and 'Quantile Set Efficacy' set the quantile cuts for all the continuous variables (Exposure metrics and Continuous Covariates) that you may need later before you step into the EDA part. You can reset your quantile cuts later whenever you want. (The default values are 4).



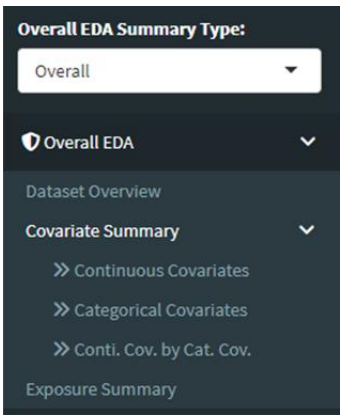
Display 3. Quantile Cuts for Continuous Variables

EXPLORATORY DATA ANALYSIS (EDA)

Overall EDA

You can use graphical and descriptive analysis for covariates and exposure metrics in this section.

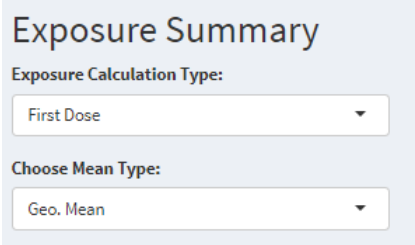
1. 'Overall EDA Summary Type' is used for the participant's selection for Overall EDA part.
   - 'Overall' for all participants in the ADER dataset
   - 'Efficacy' for participants included in ER efficacy summary.
   - 'Safety' for participants included in ER safety summary.



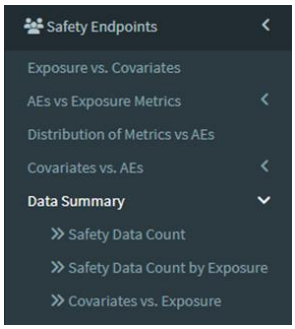
2. Covariate Summary contains 3 main parts.
   - Continuous covariates
     - Correlation matrix (Output 1)
     - Summary table by study
     - Summary table by dose (Output 2)
   - Categorical covariates
     - Summary table by study (Output 3)
     - Summary table by dose
   - Continuous Covariates by Categorical Covariates (Output 4)
3. Exposure Summary contains 3 parts.
   - Exposure Correlation (Output 5)
   - Summary table
   - Summary table by Covariates (Output 6)

   The Exposure Type contains: First Dose, Mean Dose and Mean Exposure.

   Mean Type contains: Geometric mean and arithmetic mean.



Safety Endpoints

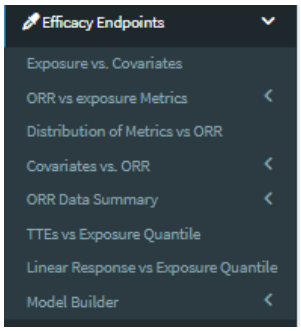


Our safety endpoints are all binary outcomes (AEs occurred or not occurred).

In Safety Endpoints Exploratory Analysis, you can get following outputs.

1. Boxplots of Exposure Metrics by Covariates (Output 7)
2. AEs occurrence rates with/without toxicity grade vs. Exposure Metrics (Output 8 & Output 9)
3. Boxplots of Exposure Metrics by AEs (Output 10)
4. Boxplots of Continuous Covariates by AEs (Output 11)
5. AEs occurrence rates vs. Categorical Covariates (Output 12)
6. Summary table for AEs occurrence rate by Exposure Metrics (Output 13)
7. Summary table for Covariates by Exposure Metrics (Output 14)

Efficacy Endpoints



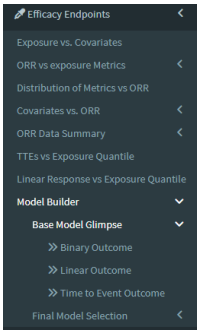
Our efficacy endpoints contain not only binary outcomes (ORR), but also linear (best percentage change from baseline sum of diameter of target lesions) and time to event (TTE) outcomes (PFS/OS/DOR).

In Efficacy Endpoints Exploratory Analysis, you can get following outputs.

1. Boxplots of Exposure Metrics by Covariates
2. ORR vs. Exposure Metrics
3. Boxplots of Exposure Metrics by ORR
4. Boxplots of Continuous Covariates by ORR
5. ORR vs. Categorical Covariates
6. Summary table for ORR and Summary table for ORR by Exposure Metrics
7. Summary table for Covariates by Exposure Metrics
8. Boxplots of PFS/OS/DOR by Exposure Metrics (Output 22)
9. Boxplots of Best Percentage Change from Baseline Sum of Diameter by Exposure Metrics (Output 23)

The outputs 1-7 aim at binary outcome ORR which are quite similar to the safety endpoints outputs.

MODEL BUILDER

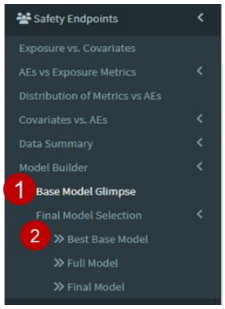


We have total 3 types of endpoints

1. Binary Outcome (AEs & ORR)
2. Continuous Outcome
3. Time to Event Outcome (PFS/OS/DOR)

Safety endpoints only have binary outcome while efficacy endpoints have all 3 types of outcomes.

Base Model (Only Exposure Metrics Included)



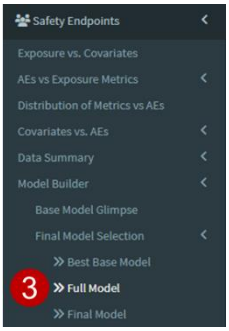
In 'Base Model Glimpse' , you can get Base Model Plots (Only contain exposure metric as predictor) (Output 15, Output 24, Output 25, Output 26).

We also add a subgroup selection function in case you want to check the stratified plots for certain subgroups.

The result of each base model will be stored and be used to select the best base model (In 'Best Base Model', you will get a summary table for all the selected exposure metric and the table will highlight the best base model for each endpoint) for later full model and final model (Output 16).

You can use log-scaled exposure by checking the Log Scaled Exposure.

Full Model (All Special Interested Covariates Included)

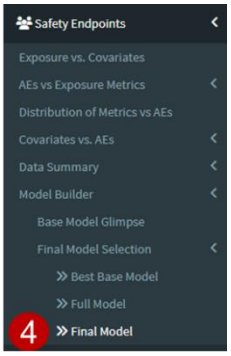


With best base model (Best Exposure metric) for each endpoint, you will now include all the covariates selected in the best base model and you can modify selected the covariates you want in this place.

You can get the estimate table, VIF check, diagnosis plots and forest plot for each binary and linear outcomes (Output 17, Output 18, Output 19, Output 20).

You can get the estimate table, independence check, influential check forest plot and Cox PH regression plot for each TTE outcome.

Final Model (Stepwise Covariate Selection)



We use backward selection process to get the final model for each endpoint based on the AIC values.

You can get model selection result (Output 21), final model coefficient estimate table, diagnosis plots and forest plot for each binary and linear outcomes.

You can get model selection result, the estimate table, independence check, influential check forest plot and Cox PH regression plot for each TTE outcomes (Output 27, Output 28, Output 29, Output 30, Output 31).

Report Generation

Another function of our E-R app is to generate the final report. Once the report has been ready the Download Report button will be activated.

You can find the 'Include Plot/Table' checkboxes above the plots or tables, and you can choose the plots or tables to be included in the final report.

By default, all the boxes are checked which means all the plots or tables will be contained in the final reports.

Display 4. Render Report and Download Report

We generate a R markdown document based on inputs in Shiny. The R markdown file is used to set the final report content and output format. The reactive values (plots, tables, datasets) created in R shiny app will be passed to rmd file and announced in the header.

The code below shows how we pass reactive values from R shiny to R markdown.

```
# R shiny code for R markdown

    observeEvent(input$covs,{
      if (!is.null(infile())){
          enable("render_report_button")
    }else{
      disable("render_report_button")
      disable("download_rendered_report")
      report_loc(NULL)
    }
  }, ignoreNULL = FALSE)

  ## Render report on click. Store result to reactive value
  report_loc <- reactiveVal()

  observeEvent(input$render_report_button,{

    ## always write to a new dir
    output_dir <- tempfile()
    dir.create(output_dir)

    ## store data from shiny in env for report, getting values from
reactive
    render_env <- new.env(parent = globalenv())
    render_env$safds <- safds()
    render_env$effds <- effds()
    ...

    params <- list(
      plots = RV$reportPlots,
      ccovname = rv$ccovname,
      estimates = rv$estimates,
      plots_ae_exp_aucfd = RV$reportPlots_ae_exp_aucfd,
      plots_ae_exp_cmaxfd = RV$reportPlots_ae_exp_cmaxfd,
      plots_ae_exp_cminfd = RV$reportPlots_ae_exp_cminfd,
      tables_saf_dt_exp = RV$reportTables_saf_dt_exp,
      tables_sumcov_saf = RV$reportTables_sumcov_saf,
      ...
    )

    ## render the report.Rmd
    render(
      input = "report.Rmd", ## capitalization must match
      output_dir = output_dir,
      params = params,
      envir = render_env
    )

    ## update report_loc to have rendered file
    report_loc(list.files(output_dir, full.names = TRUE))
  })

  ## enable downloading if report is rendered
  observeEvent(report_loc(),{
```

```
    if(!is.null(report_loc())){
      Save_done <- showNotification("Report Has been generate, Please go
and download!", duration = 5, type= "message")
      enable("download_rendered_report")
    }else{
      disable("download_rendered_report")
    }
  }, ignoreNULL = FALSE)

  ## download rendered report!
  output$download_rendered_report <- downloadHandler(
    filename = function(){
      basename(report_loc())
    },
    content = function(file){
      file.copy(report_loc(), file, overwrite = TRUE)
    }
  )
```

Code 1. R shiny code for rendering rmd and downloading output file

```
# R markdown Header
---
title: "E-R Analysis"
author: "Daniel Chu"
date: '`r format(Sys.Date(), "%B %d, %Y")`'
toctitle: "Contents"
output:
  html_document:
    code_folding: hide
    toc: true
    toc_depth: 4
    toc_float: true
    number_sections: true
    df_print: paged
    self_contained: yes
    mode: selfcontained
    editor_options:
      chunk_output_type: console
params:
  plots: NA
  ccovname: NA
  plots_ae_exp_aucfd: NA
  plots_ae_exp_cmaxfd: NA
  plots_ae_exp_cminfd: NA
  tables_saf_dt_exp: NA
  tables_sumcov_saf: NA
  ...
---
```

Code 2. R markdown header

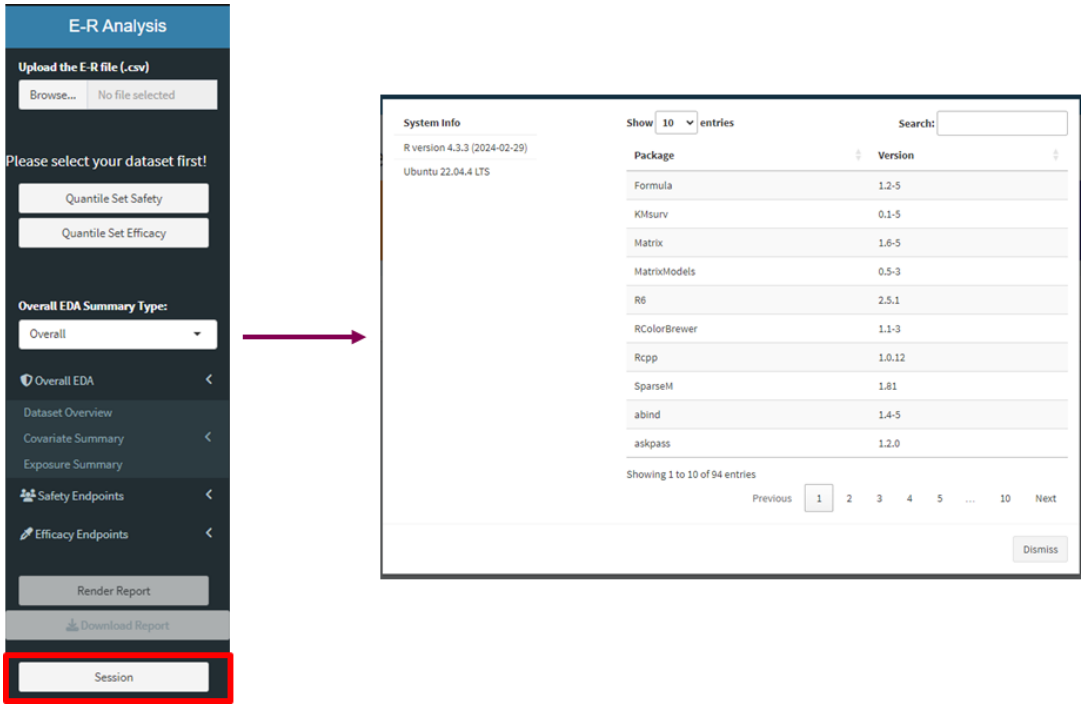
Session Information

R version: 4.3.3

shinyproxy: 3.0.2

Loaded Packages:

You can get packages information by clicking on ‘Session’ in the Sidebar Panel.



Display 5. Session Information of the App.

OUTPUTS FROM THE APP

Output 1. Correlation Plot of Continuous Covariates

Plots | Summary by Study | Summary by Dose

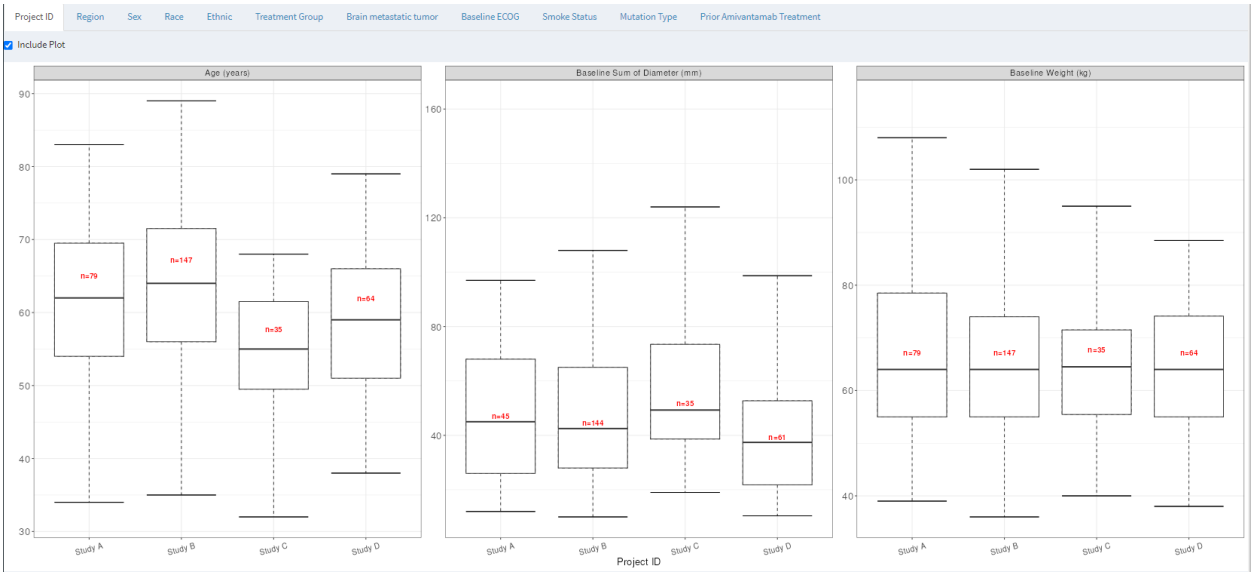
	50 mg (N=3)	100 mg (N=8)	200 mg (N=82)	300 mg (N=215)	400 mg (N=17)	Overall (N=325)
Age (years)						
Mean (SD)	47.0 (10.5)	62.8 (11.3)	61.4 (10.8)	61.1 (11.0)	55.6 (7.52)	60.8 (10.9)
Median [Min, Max]	48.0 [36.0, 57.0]	60.5 [48.0, 83.0]	62.0 [34.0, 85.0]	62.0 [32.0, 89.0]	54.0 [47.0, 72.0]	61.0 [32.0, 89.0]
Baseline Weight (kg)						
Mean (SD)	58.7 (5.69)	64.9 (19.7)	64.2 (15.4)	65.6 (13.1)	72.0 (18.1)	65.5 (14.1)
Median [Min, Max]	57.0 [54.0, 65.0]	61.8 [44.0, 94.0]	61.5 [39.0, 115]	64.0 [36.0, 108]	68.1 [49.0, 114]	64.0 [36.0, 115]
Baseline Sum of Diameter (mm)						
Mean (SD)	100 (15.6)	32.5 (6.86)	48.5 (33.0)	49.4 (30.5)	55.1 (30.2)	49.6 (31.1)
Median [Min, Max]	100 [89.0, 111]	32.5 [27.6, 37.3]	38.0 [10.0, 163]	44.8 [10.0, 162]	50.0 [17.0, 131]	42.0 [10.0, 163]
Missing	1 (33.3%)	6 (75.0%)	9 (11.0%)	20 (9.3%)	4 (23.5%)	40 (12.3%)

Output 2. Summary Table of Continuous Covariates by Dose

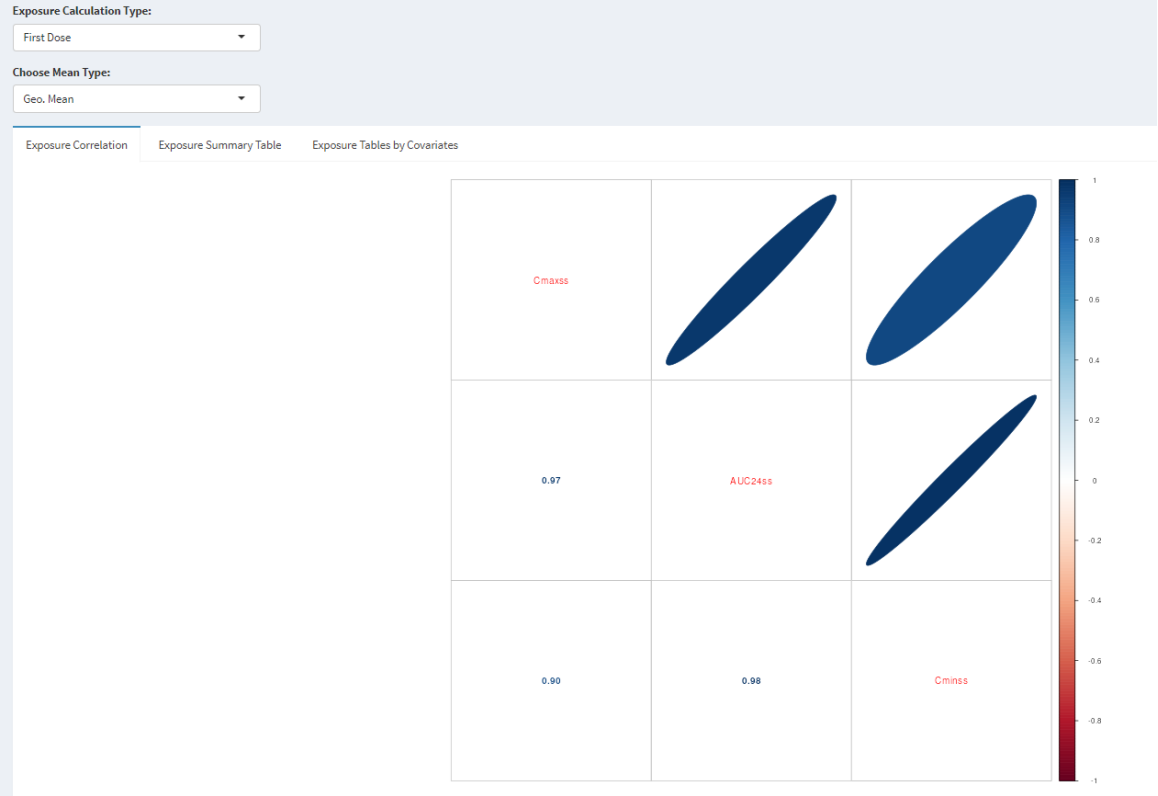
Summary by Study | Summary by Dose

	Study A (N=79)	Study B (N=147)	Study C (N=35)	Study D (N=64)	Overall (N=325)
Region					
Asia	47 (59.5%)	87 (59.2%)	35 (100%)	64 (100%)	233 (71.7%)
Non-Asia	32 (40.5%)	60 (40.8%)	0 (0%)	0 (0%)	92 (28.3%)
Sex					
F	43 (54.4%)	89 (60.5%)	15 (42.9%)	36 (56.3%)	183 (56.3%)
M	36 (45.6%)	58 (39.5%)	20 (57.1%)	28 (43.8%)	142 (43.7%)
Race					
ASIAN	58 (73.4%)	91 (61.9%)	35 (100%)	64 (100%)	248 (76.3%)
OTHER	2 (2.5%)	2 (1.4%)	0 (0%)	0 (0%)	4 (1.2%)
WHITE	19 (24.1%)	54 (36.7%)	0 (0%)	0 (0%)	73 (22.5%)
Ethnic					
HISPANIC OR LATINO	1 (1.3%)	10 (6.8%)	0 (0%)	0 (0%)	11 (3.4%)
NOT HISPANIC OR LATINO	78 (98.7%)	137 (93.2%)	35 (100%)	64 (100%)	314 (96.6%)

Output 3. Summary Table of Categorical Covariates by Study



Output 4. Boxplots of Continuous Covariates by Categorical Covariates



Output 5. 3 First Dose Exposure Metrics Correlation Plots

Exposure Calculation Type:

Mean Exposure

Choose Mean Type:

Geo. Mean

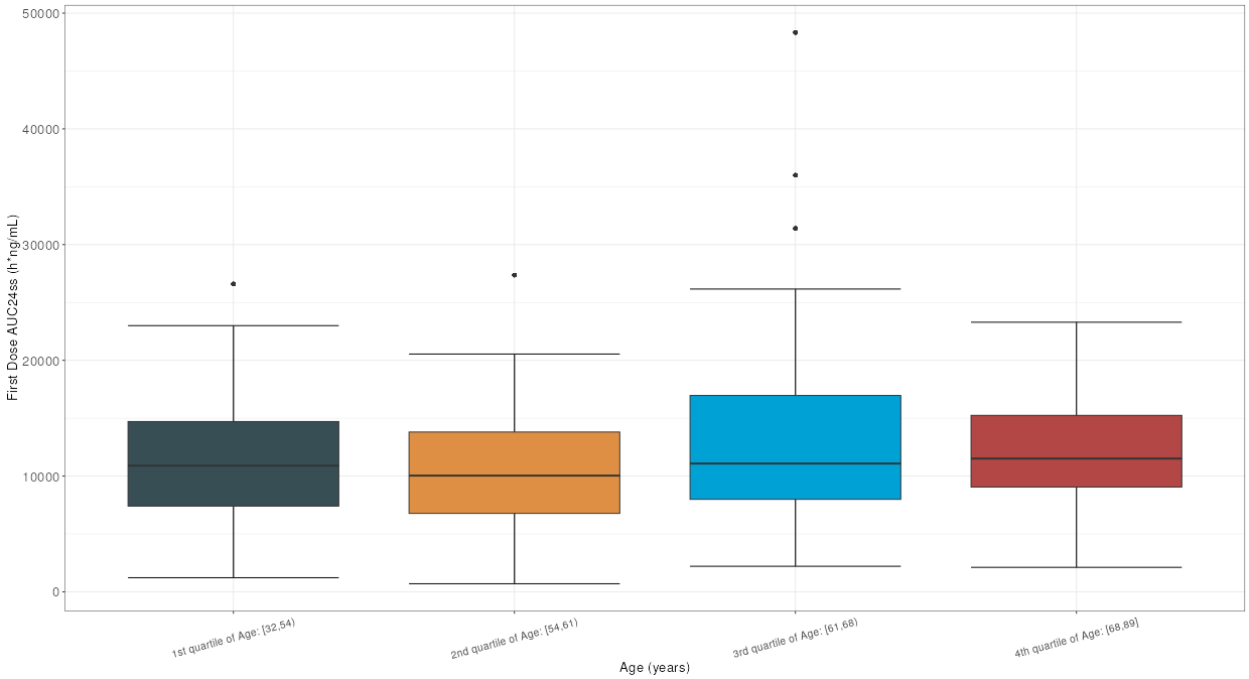
Exposure Correlation | Exposure Summary Table | Exposure Tables by Covariates

Select the covariates that you are interested:

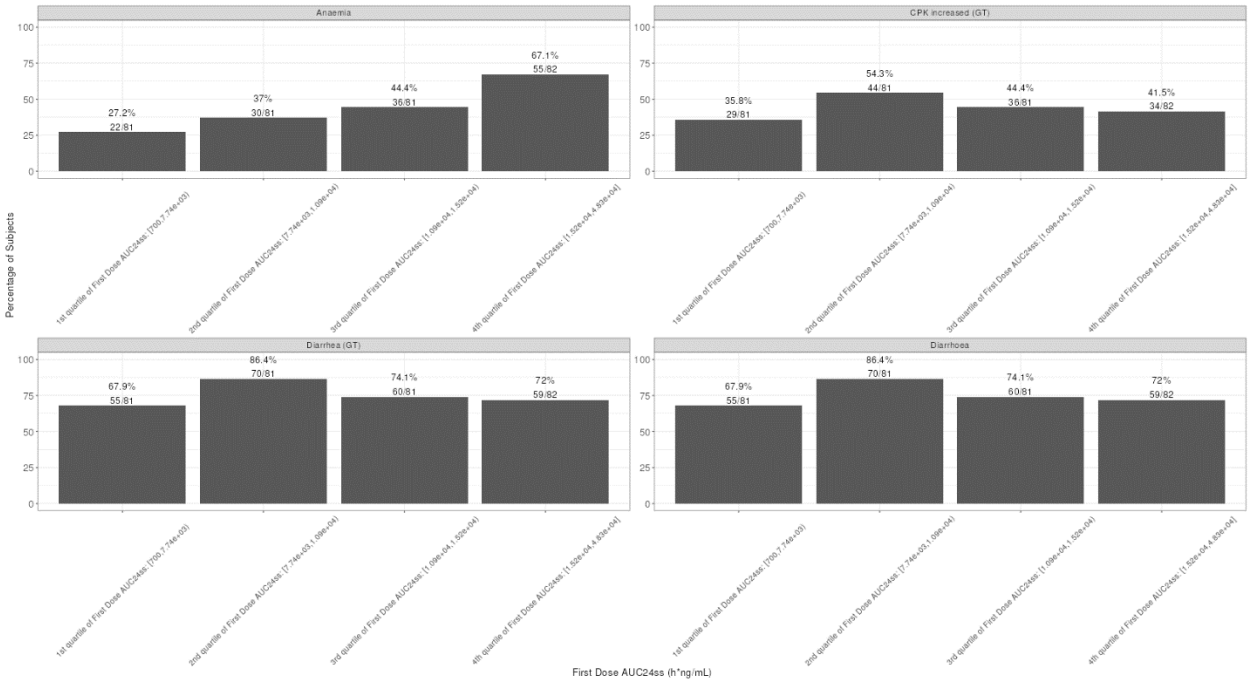
Project ID@PROJID

PROJID	Exposure Metric	n	mean (SD)	median [min,max]	q25	q50	q75
Study A	Mean Exposure AUC24 (h*ng/mL)	375	8349.2 (4248.77)	7762 [0, 23070]	5507.68	7762.05	10485.57
Study A	Mean Exposure Cmax (ng/mL)	375	458.7 (267.45)	407 [22, 1417]	279.53	407.01	546.80
Study A	Mean Exposure Cmin (ng/mL)	375	252.5 (129.88)	235 [0, 733]	169.98	234.94	326.02
Study B	Mean Exposure AUC24 (h*ng/mL)	1073	8748.8 (4101.45)	7649 [795, 24281]	5841.65	7649.18	10851.33
Study B	Mean Exposure Cmax (ng/mL)	1073	462.5 (244.82)	392 [46, 1376]	286.89	391.88	597.29
Study B	Mean Exposure Cmin (ng/mL)	1073	277.2 (132.07)	248 [16, 781]	183.42	247.71	352.89
Study C	Mean Exposure AUC24 (h*ng/mL)	184	11976.7 (5899.79)	11154 [390, 31104]	7852.93	11153.71	16357.45
Study C	Mean Exposure Cmax (ng/mL)	184	627 (334.36)	558 [21, 1837]	428.13	557.64	826.72
Study C	Mean Exposure Cmin (ng/mL)	184	372.3 (193.43)	344 [10, 999]	227.65	344.16	522.37
Study D	Mean Exposure AUC24 (h*ng/mL)	515	11003.9 (4013.97)	10304 [2876, 33166]	8528.36	10304.40	12901.07
Study D	Mean Exposure Cmax (ng/mL)	515	566.8 (206.65)	534 [127, 1525]	425.40	533.71	660.00
Study D	Mean Exposure Cmin (ng/mL)	515	352.4 (147.69)	334 [32, 1215]	267.05	334.10	419.18

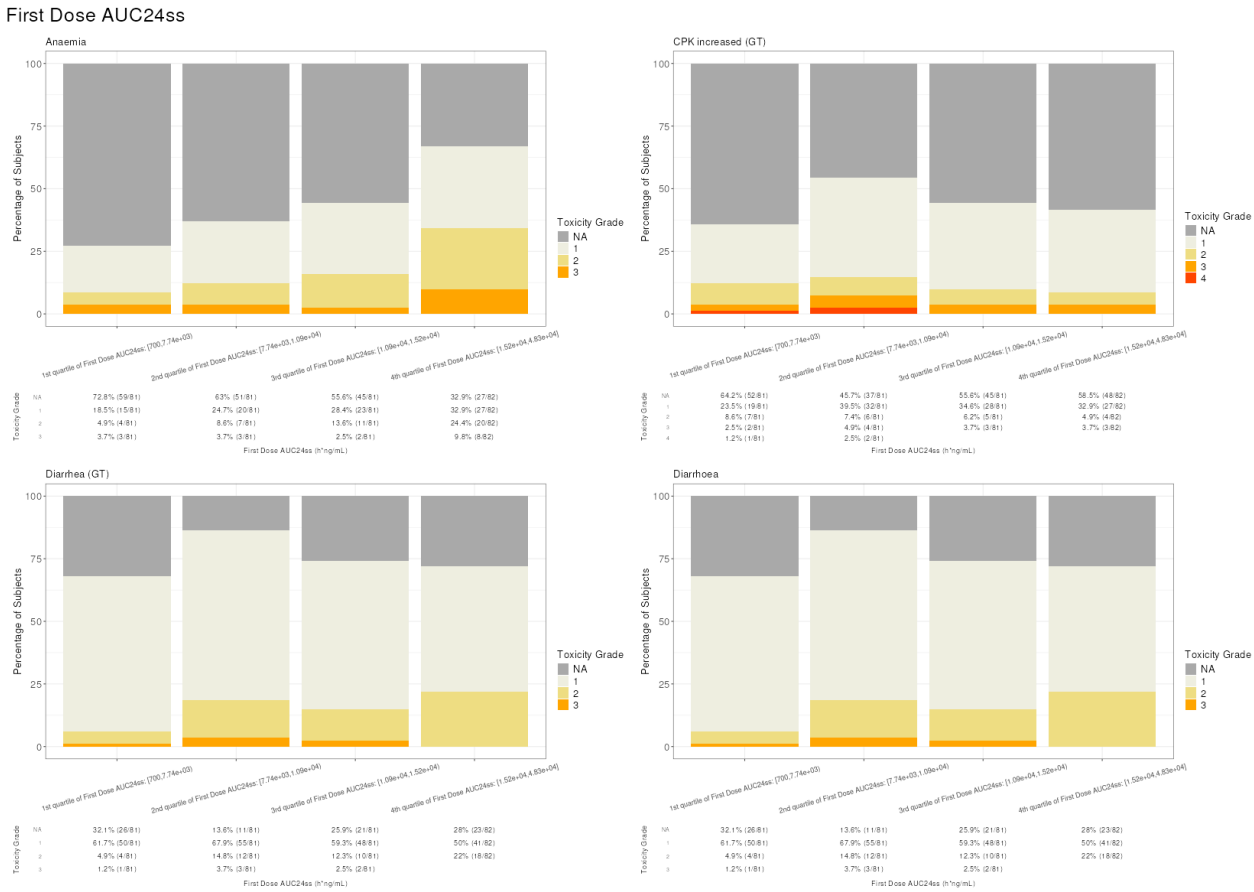
Output 6. Mean Exposure Metrics Summary table by Project ID



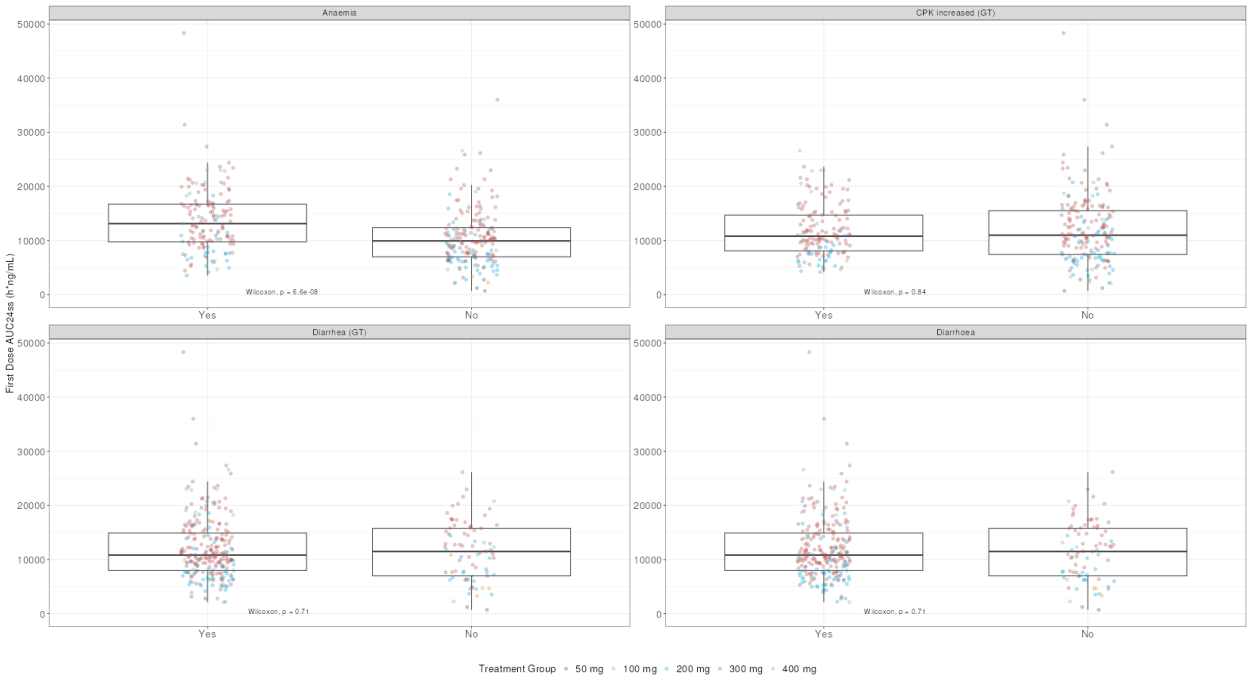
Output 7. Boxplots of First Dose $AUC_{24,\,ss}$ by Age Quartiles



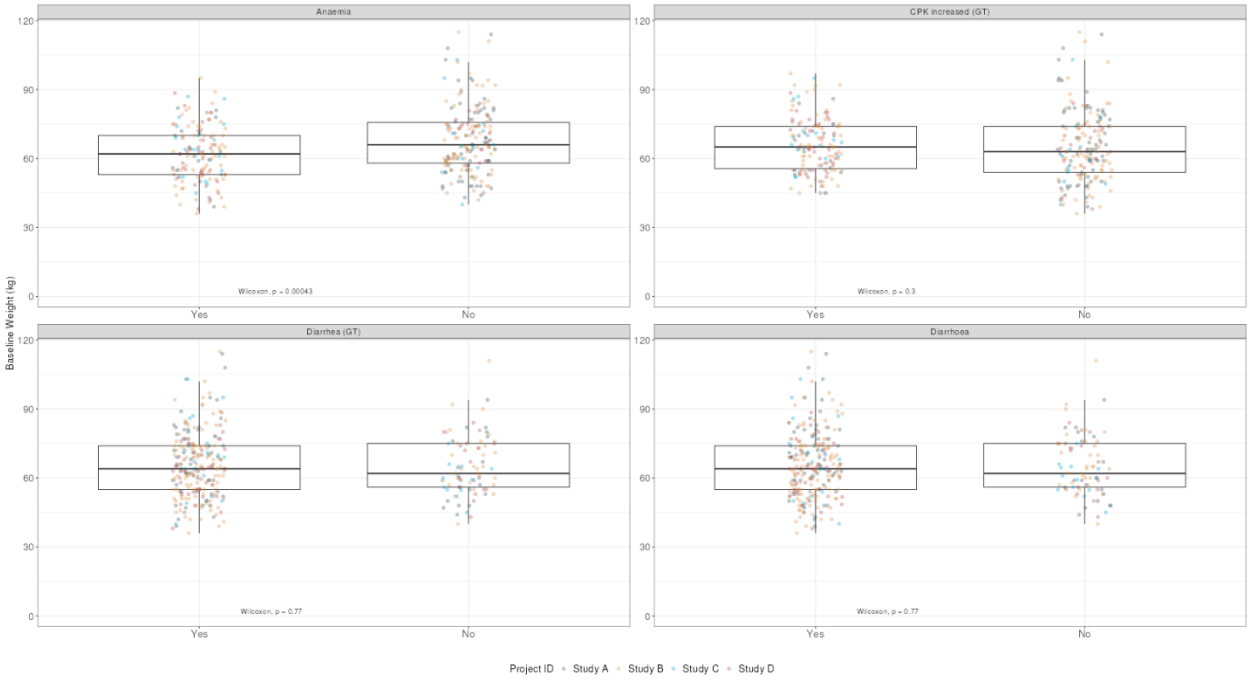
Output 8. Bar Plots of Occurrence Rate of AEs by First Dose $AUC_{24,ss}$ Quartiles



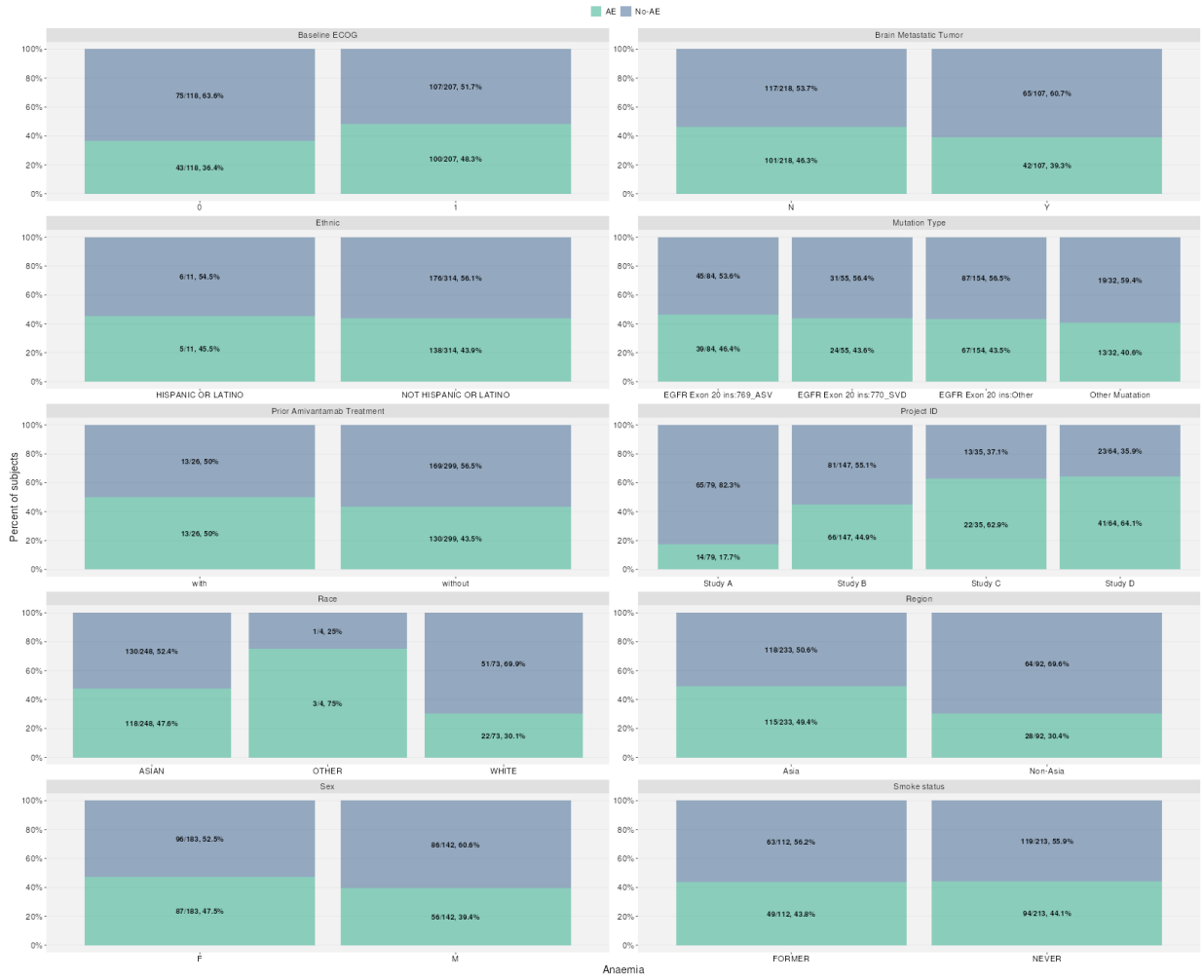
Output 9. Bar Plots of Occurrence Rate of AEs by First Dose $AUC_{24,ss}$ Quartiles with Toxicity Grade



Output 10. Boxplots of First Dose $AUC_{24, ss}$ by Occurrence of AEs



Output 11. Boxplots of baseline weight by Occurrence of AEs



Output 12. Barplots of Occurrence Rate of Anaemia by Categorical Covariates

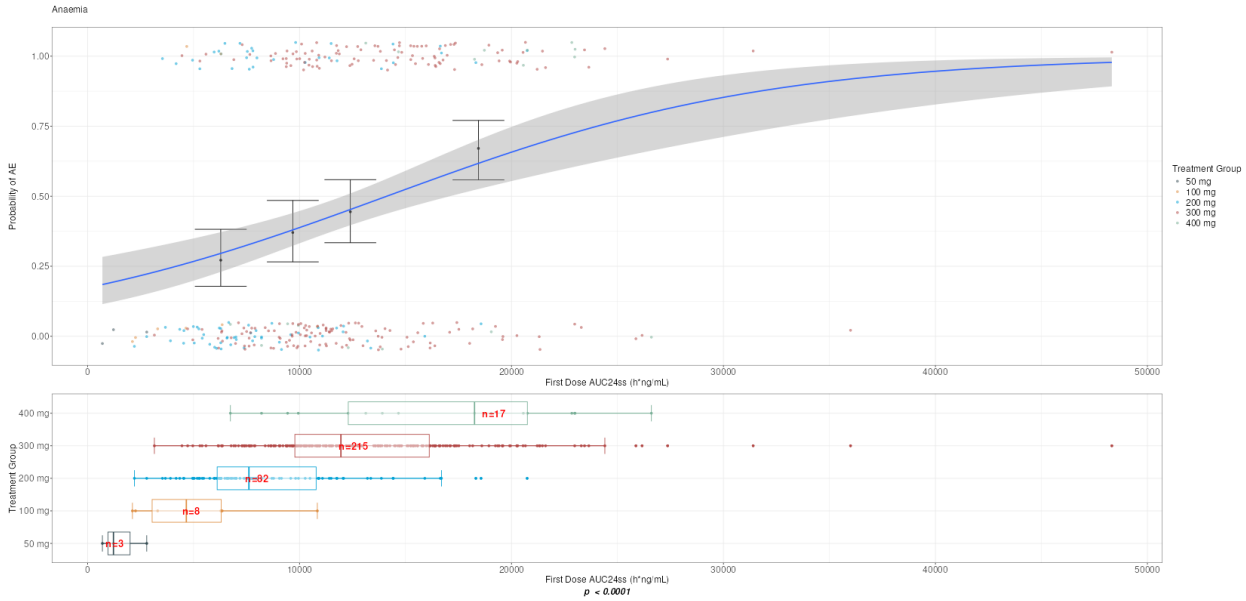
AEs' Occurrence Rate Table by Exposure quartiles

PARAM	1st quartile of First Dose AUC24ss: [700,7.74e+03)	2nd quartile of First Dose AUC24ss: [7.74e+03,1.09e+04)	3rd quartile of First Dose AUC24ss: [1.09e+04,1.52e+04)	4th quartile of First Dose AUC24ss: [1.52e+04,4.83e+04]
Anaemia	22/81 (27.2%)	30/81 (37%)	36/81 (44.4%)	55/82 (67.1%)
CPK increased (GT)	29/81 (35.8%)	44/81 (54.3%)	36/81 (44.4%)	34/82 (41.5%)
Diarrhea (GT)	55/81 (67.9%)	70/81 (86.4%)	60/81 (74.1%)	59/82 (72%)
Diarrhoea	55/81 (67.9%)	70/81 (86.4%)	60/81 (74.1%)	59/82 (72%)
Dose modified	36/81 (44.4%)	49/81 (60.5%)	49/81 (60.5%)	56/82 (68.3%)
Dose reduced	16/81 (19.8%)	28/81 (34.6%)	22/81 (27.2%)	35/82 (42.7%)
Drug interrupted	31/81 (38.3%)	38/81 (46.9%)	42/81 (51.9%)	47/82 (57.3%)
Drug withdrawn	6/81 (7.4%)	3/81 (3.7%)	16/81 (19.8%)	11/82 (13.4%)
Grade >= 3 Diarrhoea	3/81 (3.7%)	8/81 (9.9%)	8/81 (9.9%)	10/82 (12.2%)
Grade >= 3 TEAEs	39/81 (48.1%)	44/81 (54.3%)	49/81 (60.5%)	58/82 (70.7%)
Grade >=3 CPK increase	7/81 (8.6%)	13/81 (16%)	13/81 (16%)	8/82 (9.8%)
Interstitial lung disease	1/81 (1.2%)	1/81 (1.2%)	2/81 (2.5%)	3/82 (3.7%)
Nausea	23/81 (28.4%)	30/81 (37%)	28/81 (34.6%)	26/82 (31.7%)
Nausea/vomiting (GT)	32/81 (39.5%)	36/81 (44.4%)	42/81 (51.9%)	41/82 (50%)
Paronychia	26/81 (32.1%)	32/81 (39.5%)	25/81 (30.9%)	30/82 (36.6%)
Pneumonitis	0/81 (0%)	1/81 (1.2%)	1/81 (1.2%)	2/82 (2.4%)
Pneumonitis/ILD (GT)	1/81 (1.2%)	2/81 (2.5%)	3/81 (3.7%)	5/82 (6.1%)
Rash	26/81 (32.1%)	33/81 (40.7%)	39/81 (48.1%)	45/82 (54.9%)
Rash (GT)	48/81 (59.3%)	57/81 (70.4%)	55/81 (67.9%)	53/82 (64.6%)
Serious TEAEs	21/81 (25.9%)	19/81 (23.5%)	36/81 (44.4%)	35/82 (42.7%)
Stomatitis	14/81 (17.3%)	18/81 (22.2%)	16/81 (19.8%)	10/82 (12.2%)
Stomatitis (GT)	32/81 (39.5%)	35/81 (43.2%)	28/81 (34.6%)	25/82 (30.5%)
Vomiting	21/81 (25.9%)	20/81 (24.7%)	34/81 (42%)	32/82 (39%)

Output 13. AEs' Occurrence Rate Table by First Dose $AUC_{24,\,ss}$ Quartiles

	1st quartile of First Dose AUC24ss: [700,7.74e+03) (N=81)	2nd quartile of First Dose AUC24ss: [7.74e+03,1.09e+04) (N=81)	3rd quartile of First Dose AUC24ss: [1.09e+04,1.52e+04) (N=81)	4th quartile of First Dose AUC24ss: [1.52e+04,4.83e+04] (N=82)	Overall (N=325)
Project ID					
Study A	22 (27.2%)	25 (30.9%)	18 (22.2%)	14 (17.1%)	79 (24.3%)
Study B	48 (59.3%)	33 (40.7%)	34 (42.0%)	32 (39.0%)	147 (45.2%)
Study C	7 (8.6%)	5 (6.2%)	6 (7.4%)	17 (20.7%)	35 (10.8%)
Study D	4 (4.9%)	18 (22.2%)	23 (28.4%)	19 (23.2%)	64 (19.7%)
Region					
Asia	55 (67.9%)	56 (69.1%)	56 (69.1%)	66 (80.5%)	233 (71.7%)
Non-Asia	26 (32.1%)	25 (30.9%)	25 (30.9%)	16 (19.5%)	92 (28.3%)
Age (years)					
Mean (SD)	58.3 (10.1)	61.4 (10.6)	60.6 (12.1)	62.7 (10.5)	60.8 (10.9)
Median [Min, Max]	58.0 [32.0, 85.0]	63.0 [35.0, 82.0]	62.0 [34.0, 84.0]	64.0 [38.0, 89.0]	61.0 [32.0, 89.0]
Sex					
F	44 (54.3%)	47 (58.0%)	49 (60.5%)	43 (52.4%)	183 (56.3%)
M	37 (45.7%)	34 (42.0%)	32 (39.5%)	39 (47.6%)	142 (43.7%)
Race					
ASIAN	58 (71.6%)	61 (75.3%)	61 (75.3%)	68 (82.9%)	248 (76.3%)
WHITE	23 (28.4%)	19 (23.5%)	19 (23.5%)	12 (14.6%)	73 (22.5%)
OTHER	0 (0%)	1 (1.2%)	1 (1.2%)	2 (2.4%)	4 (1.2%)
Ethnic					
HISPANIC OR LATINO	3 (3.7%)	2 (2.5%)	3 (3.7%)	3 (3.7%)	11 (3.4%)
NOT HISPANIC OR LATINO	78 (96.3%)	79 (97.5%)	78 (96.3%)	79 (96.3%)	314 (96.6%)

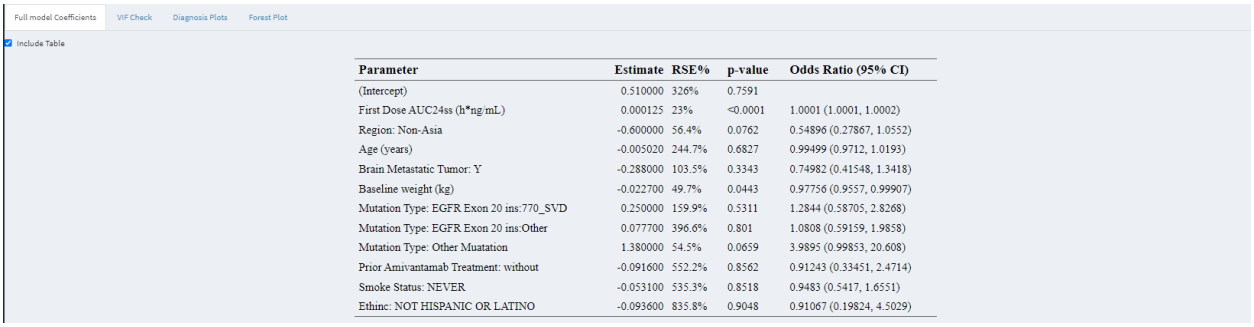
Output 14. Summary Table of Covariates by First Dose $AUC_{24,\ ss}$ Quartiles



Output 15. Model-Predicted Probability of Response of Anaemia by First Dose $AUC_{24,\ ss}$

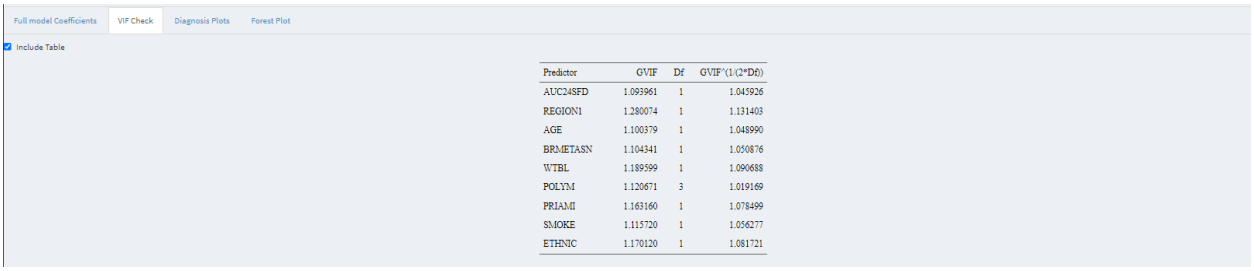
AE	Group	Log Scaled	Estimate	p.value	AIC	Best_AIC	Parameter
Anaemia	First Dose AUC24ss (h*ng/mL)-Anaemia	FALSE	0.000110684315980	< 0.0001	423.01555	422.01296	Slope (1/(ng/mL))
Anaemia	Mean Exposure AUC24 (h*ng/mL)-Anaemia	FALSE	0.000138835010746	< 0.0001	422.01296	422.01296	Slope (1/(ng/mL))
CPK increased (GT)	First Dose AUC24ss (h*ng/mL)-CPK increased (GT)	FALSE	-0.000004107060667	0.8325	449.80958	449.12687	Slope (1/(ng/mL))
CPK increased (GT)	Mean Exposure AUC24 (h*ng/mL)-CPK increased (GT)	FALSE	0.000020605254576	0.3940	449.12687	449.12687	Slope (1/(ng/mL))

Output 16. Best Base Model for AEs



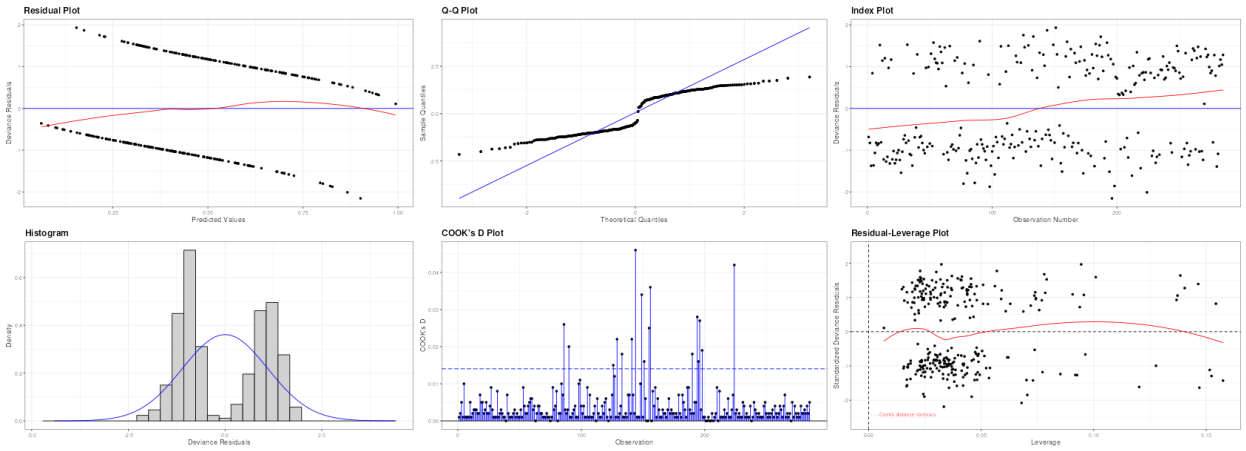
Parameter	Estimate	RSE%	p-value	Odds Ratio (95% CI)
(Intercept)	0.510000	326%	0.7591	
First Dose AUC24ss (h*ng/mL)	0.000125	23%	<0.0001	1.0001 (1.0001, 1.0002)
Region: Non-Asia	-0.600000	56.4%	0.0762	0.54896 (0.27867, 1.0552)
Age (years)	-0.005020	244.7%	0.6827	0.99499 (0.9712, 1.0193)
Brain Metastatic Tumor: Y	-0.288000	103.5%	0.3343	0.74982 (0.41548, 1.3418)
Baseline weight (kg)	-0.022700	49.7%	0.0443	0.97756 (0.9557, 0.99907)
Mutation Type: EGFR Exon 20 ins:770_SVD	0.250000	159.9%	0.5311	1.2844 (0.58705, 2.8268)
Mutation Type: EGFR Exon 20 ins:Other	0.077700	396.6%	0.801	1.0808 (0.59159, 1.9858)
Mutation Type: Other Muatation	1.380000	54.5%	0.0659	3.9895 (0.99853, 20.608)
Prior Amivantamab Treatment: without	-0.091600	552.2%	0.8562	0.91243 (0.33451, 2.4714)
Smoke Status: NEVER	-0.053100	535.3%	0.8518	0.9483 (0.5417, 1.6551)
Ethinc: NOT HISPANIC OR LATINO	-0.093600	835.8%	0.9048	0.91067 (0.19824, 4.5029)

Output 17. Full Model Coefficients' Result of Anaemia

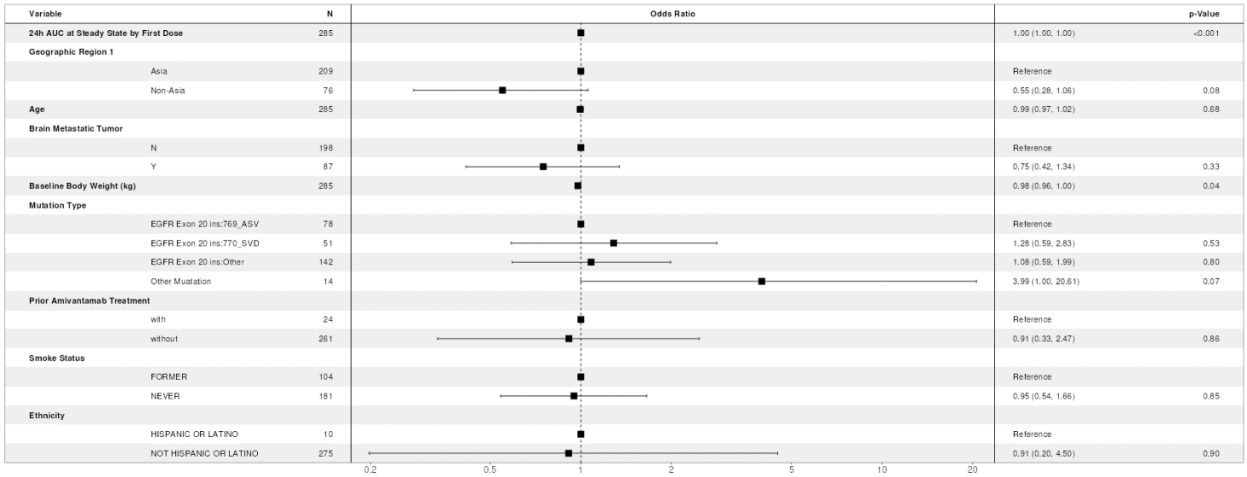


Predictor	GVIF	Df	GVIF^(1/(2*Df))
AUC24SFD	1.093961	1	1.045926
REGION1	1.280074	1	1.131403
AGE	1.100379	1	1.048990
BRMETASN	1.104341	1	1.050876
WTBL	1.189599	1	1.090688
POLYM	1.120671	3	1.019169
PRIAMI	1.163160	1	1.078499
SMOKE	1.115720	1	1.056277
ETHNIC	1.170120	1	1.081721

Output 18. Full Model VIF Check Result of Anaemia



Output 19. Diagnosis Plots for Full Model of Anaemia

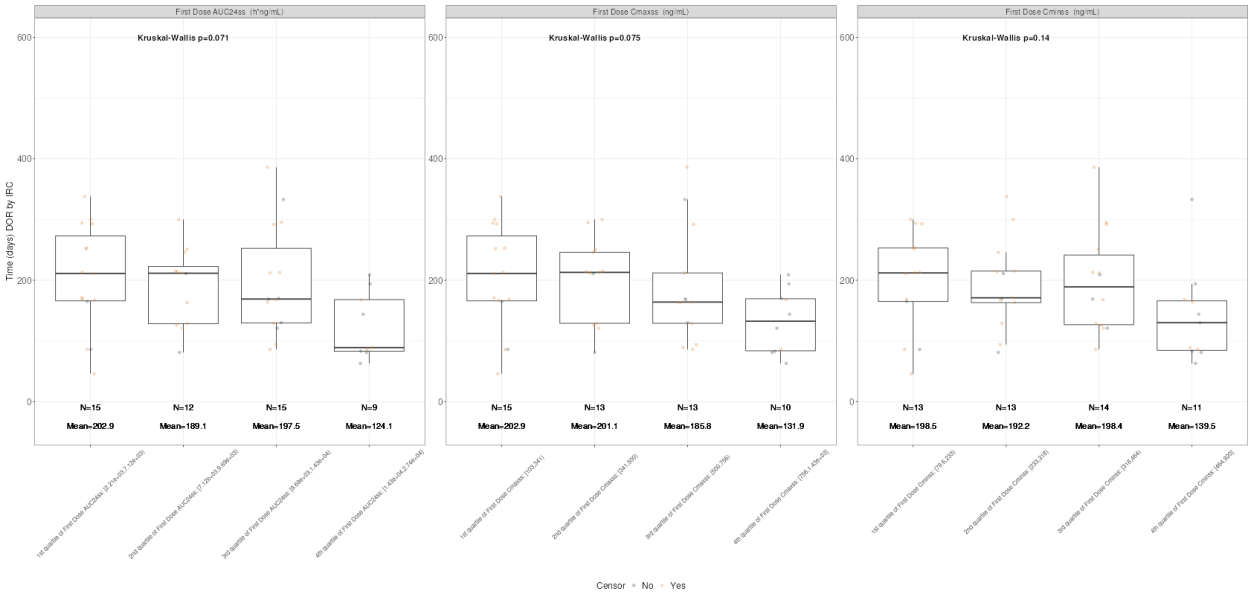


Output 20. Forest Plot for Full Model of Anaemia

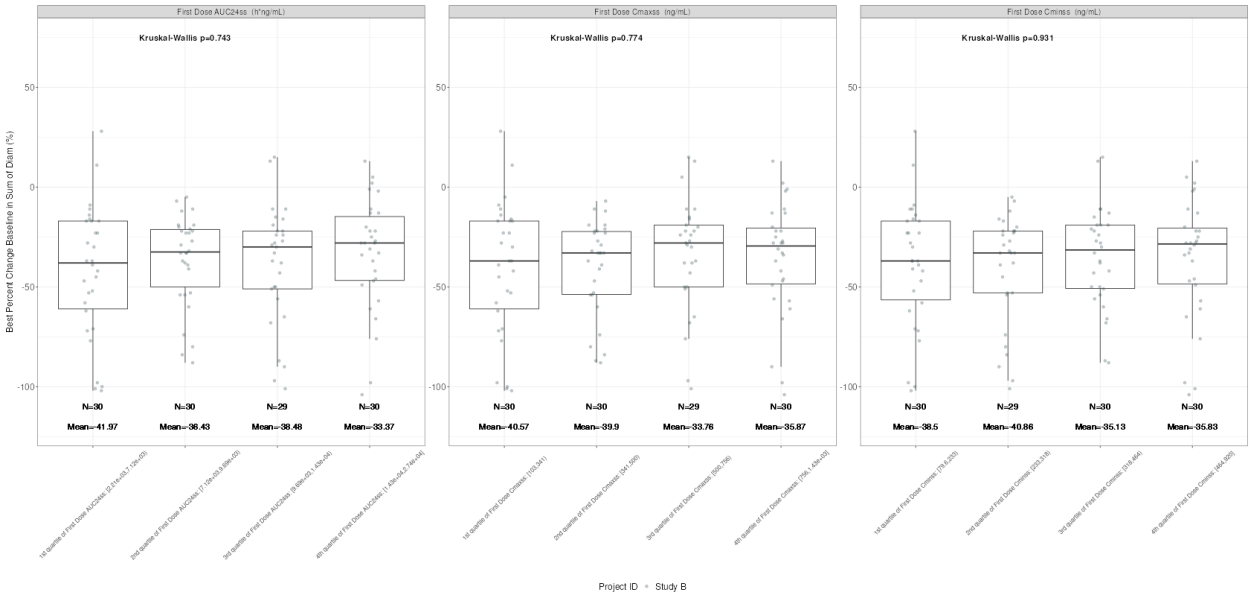
Model Selection Results | Full Model Coefficients | Diagnosis Plots | Forest Plot

```
Stepwise Model Path
Analysis of Deviance Table

Initial Model:
AVAL ~ AUC24SFD + REGION1 + AGE + BRMETASN + WTBL + POLYM + PRIAMI +
    SMOKE + ETHNIC

Final Model:
AVAL ~ AUC24SFD + REGION1 + WTBL


        Step Df   Deviance Resid. Df Resid. Dev      AIC
1                              273   346.6063 370.6063
2    - ETHNIC  1 0.01426790       274   346.6206 368.6206
3    - PRIAMI  1 0.02863645       275   346.6492 366.6492
4     - SMOKE  1 0.02764084       276   346.6768 364.6768
5       - AGE  1 0.16267958       277   346.8395 362.8395
6     - POLYM  3 4.31769055       280   351.1572 361.1572
7 - BRMETASN  1 0.79173850       281   351.9489 359.9489
```

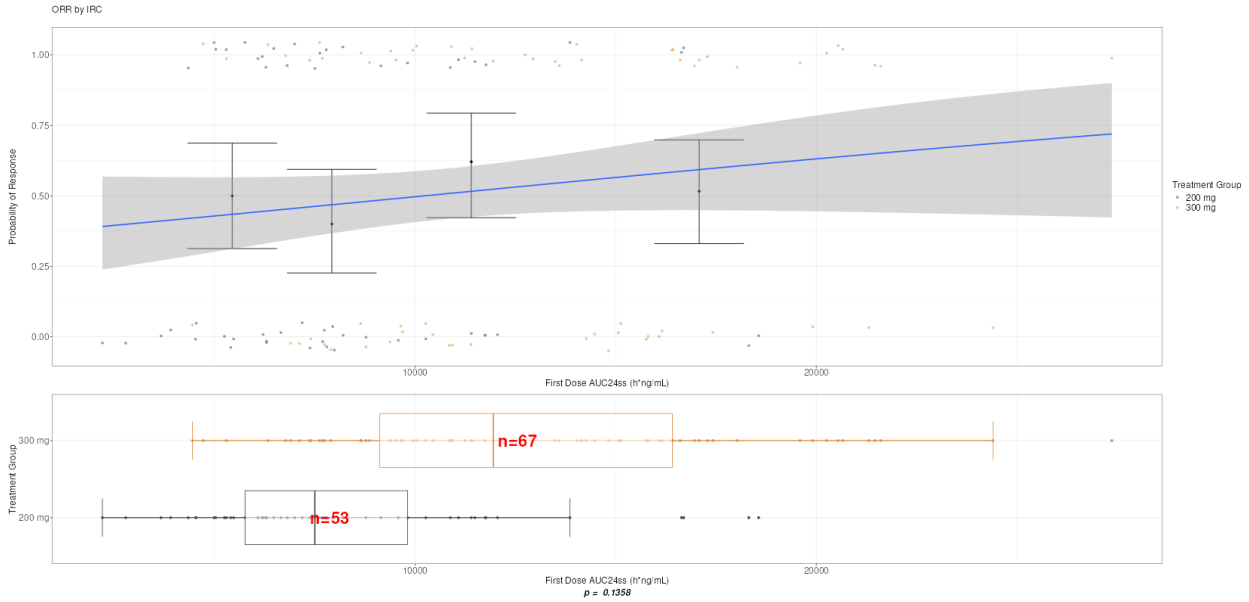
Output 21. Backward Selection Result for Final Model of Anaemia



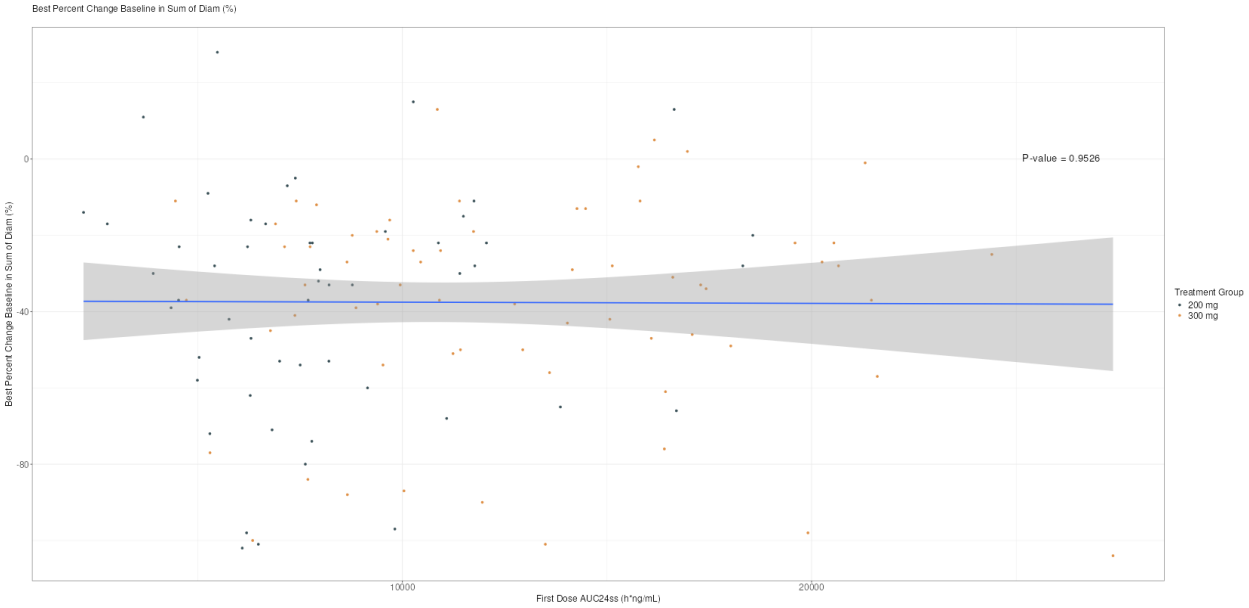
Output 22. Boxplots of DOR time by First Dose $AUC_{24,\ ss}$, $Cmax_{ss}$, $Cmin_{ss}$



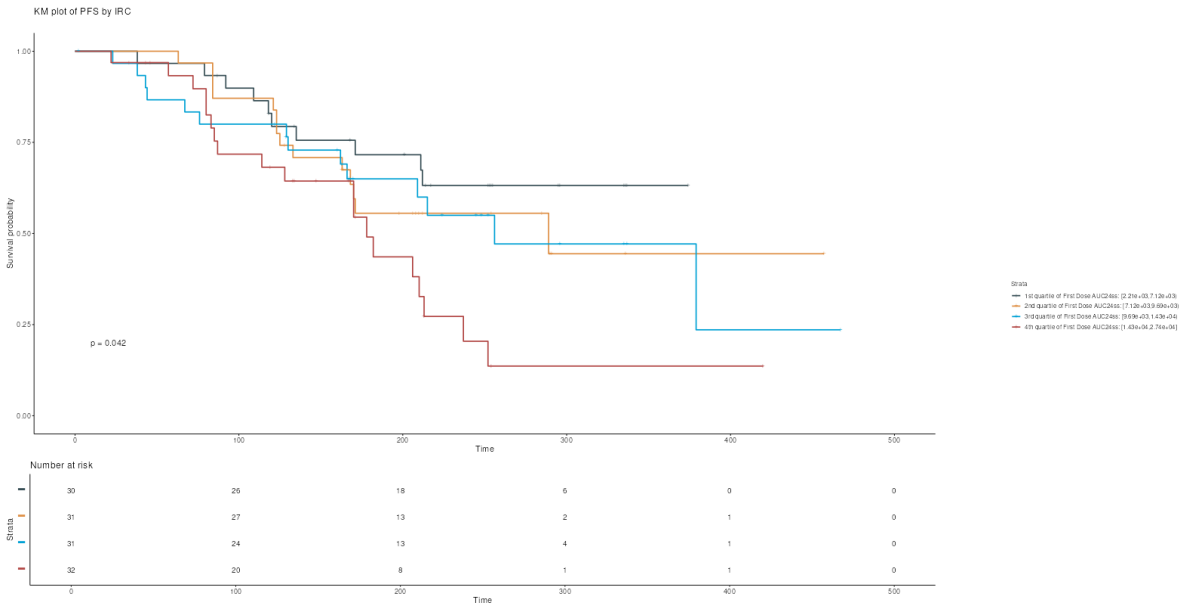
Output 23. Boxplots of Best Percentage Chage from Baseline Sum of Diameter of Target Lesions by First Dose $AUC_{24,\ ss}$, $Cmax_{ss}$, $Cmin_{ss}$



Output 24. Model-Predicted ORR by First Dose AUC24, ss



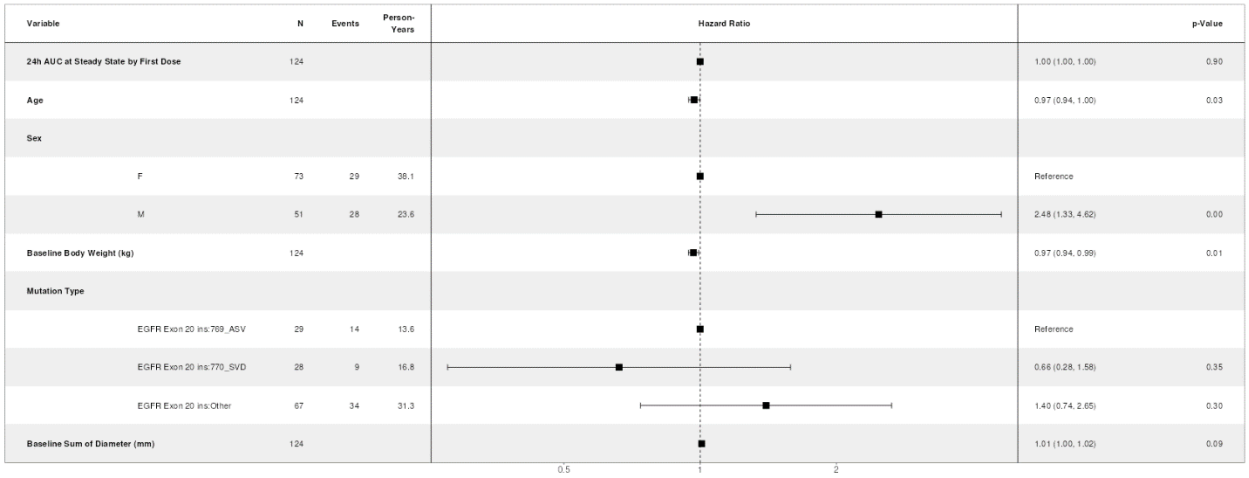
Output 25. Model-Predicted Best Percentage Chage from Baseline Sum of Diameter of Target Lesions by First Dose AUC24, ss



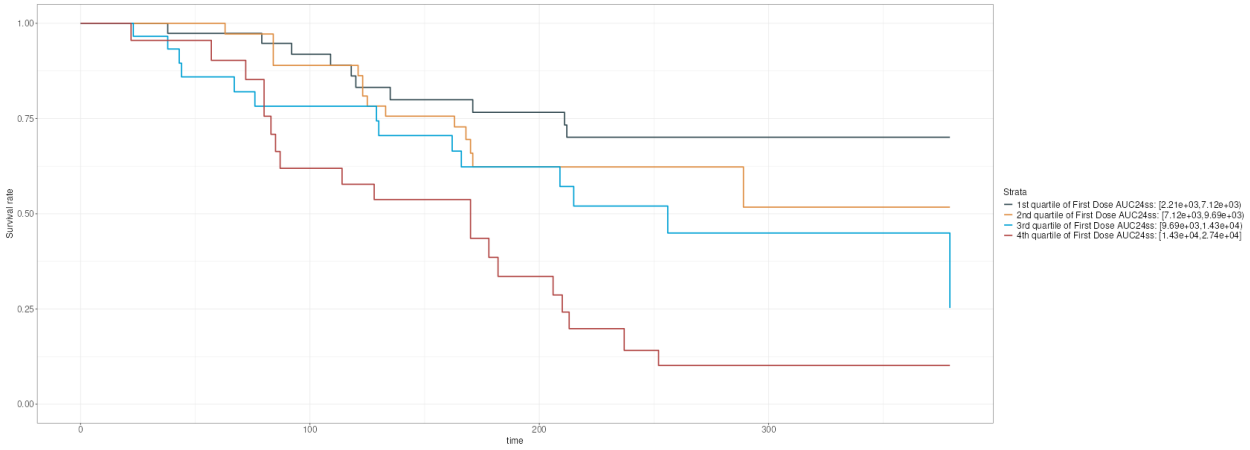
Output 26. KM Plot of PFS Stratified by First Dose AUC24, ss Quartiles

Parameter	Estimate	RSE%	p-value	Hazard Ratio (95% CI)
First Dose AUC24ss (h*ng/mL)	0.00000373	770.5%	0.8967	1 (0.99995, 1.0001)
Age (years)	-0.03070000	46.9%	0.0331	0.9698 (0.94283, 0.99754)
Sex: M	0.90800000	35%	0.0043	2.4791 (1.3298, 4.6215)
Baseline weight (kg)	-0.03430000	38.7%	0.0098	0.96632 (0.94152, 0.99178)
Mutation Type: EGFR Exon 20 ins:770_SVD	-0.41200000	107.9%	0.3540	0.66221 (0.27698, 1.5832)
Mutation Type: EGFR Exon 20 ins:Other	0.33500000	97.2%	0.3035	1.3981 (0.73844, 2.647)
Baseline Sum of Diameter (mm)	0.00763000	59.3%	0.0916	1.0077 (0.99877, 1.0166)

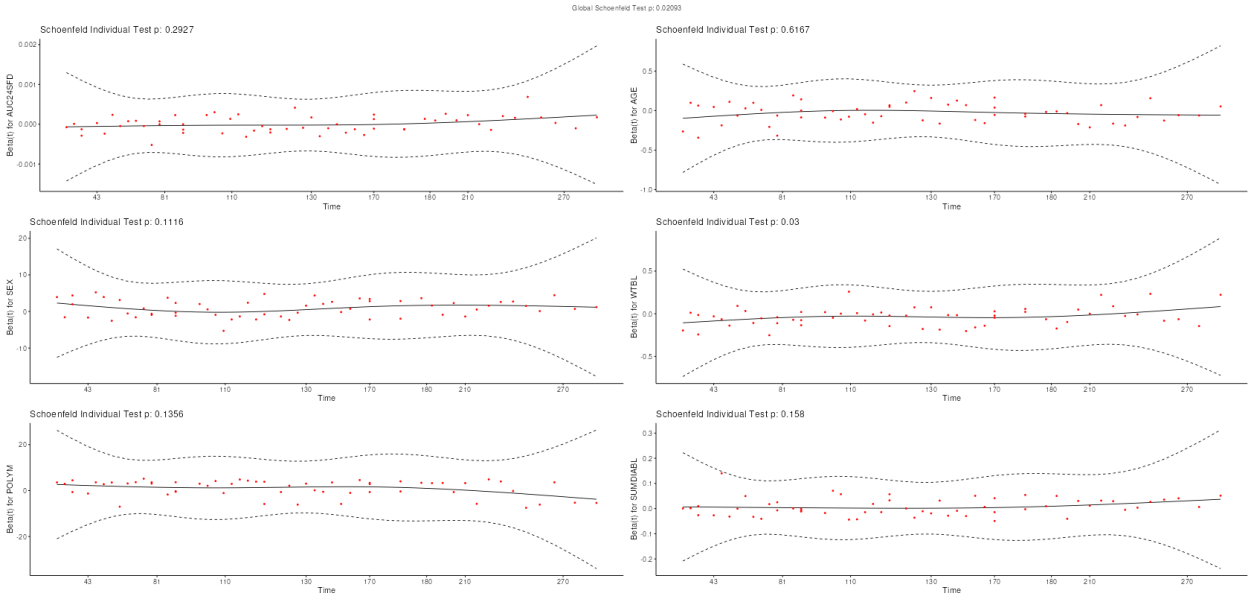
Output 27. Estimates of Final Model Coefficients



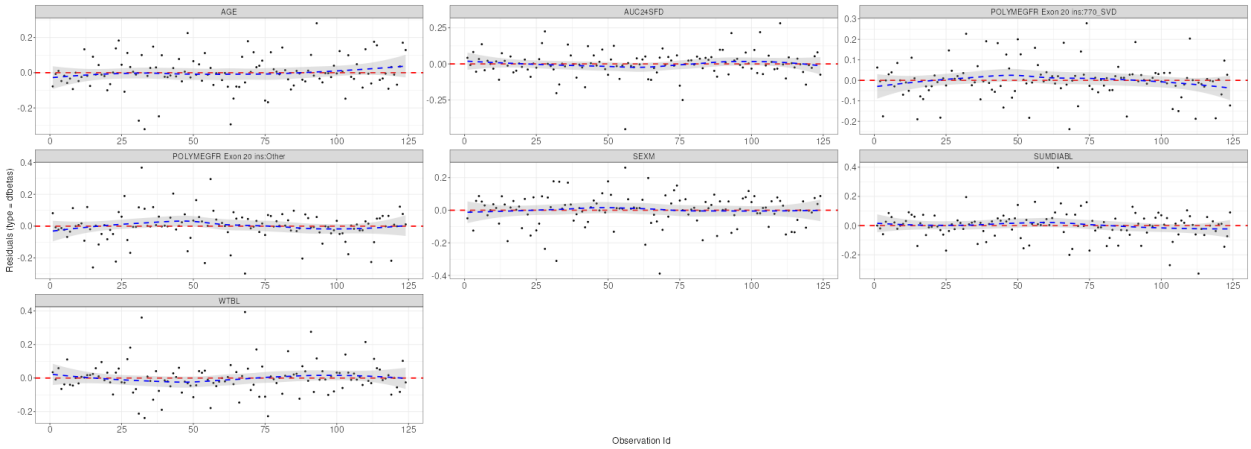
Output 28. Forest Plot for Final Model of Anaemia



Output 29. Cox PH Regression Plot of PFS Stratified by First Dose AUC24, ss Quartiles



Output 30. Schoenfeld Individual Tests for Final Model Independence Check



Output 31. Residual Plots for Influence Check of Final Model

CONCLUSION

This paper describes the E-R statistical analysis method, the construction of analysis dataset (ADER), the usage of our E-R platform and the tables and figures generated by the app. In the next step, we will further optimize the function of report generation and automatically generate standardized word and pdf format reports.

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[1] https://shiny.posit.co/r/gallery/

[2] https://rstudio.github.io/shinydashboard/

[3] https://rmarkdown.rstudio.com/

[4] https://www.shinyproxy.io/

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