Explore covariates of the signature

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Load patient data

```
load("COIN_Final.Rdata")
patient_data$SurvObj.pfs <- with(patient_data, Surv(pfstime, pfsevent))
patient_data$SurvObj.os <- with(patient_data, Surv(ostime, osevent))
```

Encode, Impute Covariates

Isolate those covariates known to be needed for Risk Signatures etc. Impute by replacing NA by the average of other patients.

```
encoded_data <- with(patient_data, data.frame(SUMLES, WBC, NEUT, SHB0, FRET, FRET.cohort))

encoded_data$RAS.Mutation <- ifelse(patient_data$RAS=="Mutation", 1, 0)
encoded_data$mlivonly <- ifelse(patient_data$mlivonly=="Yes", 1, 0)
encoded_data$PIK3CA.Mutation <- ifelse(patient_data$PIK3CA=="Mutation", 1, 0)

# Get means from the 398
df <- encoded_data[encoded_data$FRET.cohort==1,]
df <- subset(df, select = -c(FRET.cohort))
trained_means <- colMeans(df, na.rm = T)

# remove FREt.cohort col
encoded_data <- subset(encoded_data, select = -c(FRET.cohort))

# Apply to all data
#encoded_data[] <- lapply(encoded_data, NA2mean)
encoded_data[] <- replaceNA(encoded_data, trained_means)
```

Load risk signature classifier

```
Class_Predictor <-
  read.table("SP_Classifier_Score/COIN_withFRET_July16/RiskScore_formula.txt",
                        sep = '*', col.names = c("Weight", "Covariate"),
                        stringsAsFactors = F, skip = 2, fill = T)

kable(Class_Predictor)
```

Weight	Covariate
S=(0.006338408651)	SUMLES
+ (-0.142238099638)	WBC
+ (0.211925854316)	NEUT
+ (0.769846490411)	SHB0
+ (9.895611265279)	FRET
+ (-0.728162098653)	mlivonly

Weight	Covariate
+ (-1.151128618935) - (0.697856603639)	PIK3CA.Mutation

```
# Load output from Saddle Point Signature and tidy up
Class_Predictor_Betas <-
  read.table("SP_Classifier_Score/COIN_withFRET_July16/SETCV_L2/betas_with_errors_optimised.txt",
             sep = ' ', col.names = c("Covariate", "beta", "pm", "error",
                                      "rank", "z.score", "p.value"),
             stringsAsFactors = F)

Class_Predictor_Betas <- subset(Class_Predictor_Betas, select=-pm)
Class_Predictor_Betas$Covariate <- sub(":$", "", Class_Predictor_Betas$Covariate)
Class_Predictor_Betas$beta <- as.numeric(
  sub("^beta\\[\\d+]=", "", Class_Predictor_Betas$beta))
Class_Predictor_Betas$rank <- last_number(Class_Predictor_Betas$rank,
                                          decimals = F, negs = F)
Class_Predictor_Betas$z.score <- last_number(Class_Predictor_Betas$z.score,
                                          decimals = T, negs = F)
Class_Predictor_Betas$p.value <- last_number(Class_Predictor_Betas$p.value,
                                          decimals = T, negs = F)

# Create new cols as required
Class_Predictor_Betas$description <- Class_Predictor_Betas$Covariate
Class_Predictor_Betas$description <-
  sub("SUMLES", "Sum of longest diameter", Class_Predictor_Betas$description)
Class_Predictor_Betas$description <-
  sub("WBC", "White blood cell count", Class_Predictor_Betas$description)
Class_Predictor_Betas$description <-
  sub("NEUT", "Neutrophil count", Class_Predictor_Betas$description)
Class_Predictor_Betas$description <-
  sub("SHBO", "Haemaglobin (CTC grade)", Class_Predictor_Betas$description)
#Class_Predictor_Betas$description <-
#  sub("FRET", "ErbB2-ErbB3 FRET efficiency", Class_Predictor_Betas$description)
Class_Predictor_Betas$description <-
  sub("mlivonly", "Liver-only metastases", Class_Predictor_Betas$description)
Class_Predictor_Betas$description <-
  sub("PIK3CA.Mutation", "PIK3CA mutation", Class_Predictor_Betas$description)

Class_Predictor_Betas$HR <- exp(Class_Predictor_Betas$beta)
Class_Predictor_Betas$HR.U95.CI <- exp(Class_Predictor_Betas$beta+Class_Predictor_Betas$error)
Class_Predictor_Betas$HR.L95.CI <- exp(Class_Predictor_Betas$beta-Class_Predictor_Betas$error)

# Add the constant as new row
Class_Predictor_Betas <- rbind(Class_Predictor_Betas,
                               list("Constant", NA, NA, NA, NA, 0, "Constant", 1, 1, 1))

Class_Predictor_Betas$Weight <- Class_Predictor$Weight
Class_Predictor_Betas$Weight <- str_remove(Class_Predictor_Betas$Weight, "S=\\(")
Class_Predictor_Betas$Weight <- str_remove(Class_Predictor_Betas$Weight, "\\+ \\(")
Class_Predictor_Betas$Weight <- sub("\\- \\(", "-", Class_Predictor_Betas$Weight)
Class_Predictor_Betas$Weight <- str_remove(Class_Predictor_Betas$Weight, "\\)")
Class_Predictor_Betas$Weight <- as.numeric(Class_Predictor_Betas$Weight)
```

Calculate Total Risk Score

```
patient_data$Class_Pred_Score <- calculateRiskScore(Class_Predictor, encoded_data)
```

Calculate Residual Risk Scores

```
patient_data$FRET_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="FRET"), enco
patient_data$SUMLES_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="SUMLES"), 
patient_data$WBC_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="WBC"), encode
patient_data$NEUT_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="NEUT"), enco
patient_data$SHBO_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="SHBO"), enco
patient_data$mlivonly_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="mlivonly
patient_data$PIK3CA.Mutation_Residual_Score <- calculateRiskScore(subset(Class_Predictor, Covariate!="P
```

ROC

ROC curve for the 398 training data, these are the ones that we have ground truth FRET OS Class for.

```
library(pROC)
```

```
## Warning: package 'pROC' was built under R version 3.5.3
```

```
## Type 'citation("pROC")' for a citation.
```

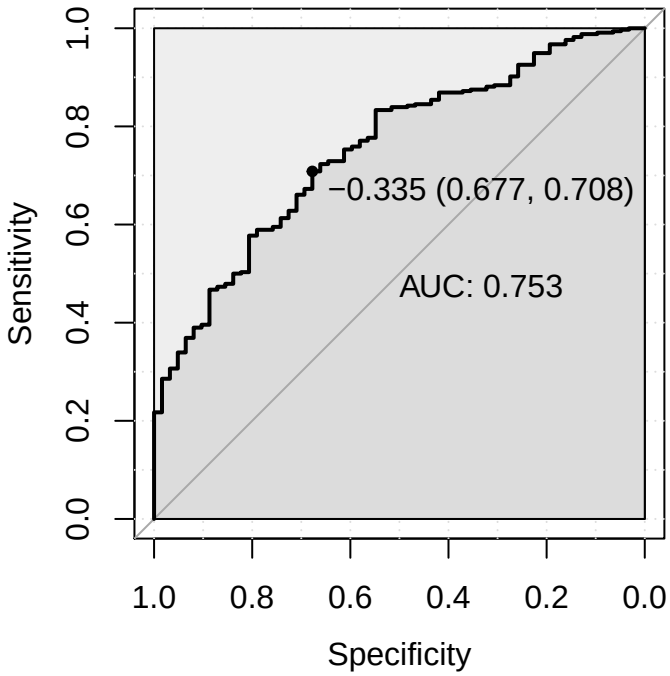
```
##
## Attaching package: 'pROC'
```

```
## The following objects are masked from 'package:stats':
##
##     cov, smooth, var
```

```
pROC_obj <- roc(patient_data$Class.FRET.OS, patient_data$Class_Pred_Score,
            smoothed = TRUE,
            # arguments for ci
            ci=FALSE, ci.alpha=0.9, stratified=FALSE,
            # arguments for plot
            plot=TRUE, auc.polygon=TRUE, max.auc.polygon=TRUE, grid=TRUE,
            print.auc=TRUE, print.thres=TRUE)
```

```
## Setting levels: control = 1, case = 2
```

```
## Setting direction: controls < cases
```



Choose an optimal threshold

```
optimal <- coords(pROC_obj, x="best", input="threshold", best.method="youden")
```

```
## Warning in coords.roc(pROC_obj, x = "best", input = "threshold",
## best.method = "youden"): An upcoming version of pROC will set the
## 'transpose' argument to FALSE by default. Set transpose = TRUE explicitly
## to keep the current behavior, or transpose = FALSE to adopt the new one
## and silence this warning. Type help(coords_transpose) for additional
## information.
```

```
optimal
```

```
##   threshold specificity sensitivity
##  -0.3347168   0.6774194   0.7083333
```

```
threshold = optimal[1]
```

Classify all patients according to predicted LCA Class

```
patient_data$Pred.Class <- ifelse(patient_data$Class_Pred_Score>threshold, 2, 1)
```

Investigate FRET vs its Residual Score

Get fresh data set of FRET patients

```
data <- subset(patient_data, FRET.cohort!=0)
```

Classifiy FRET patients according to raw FRET

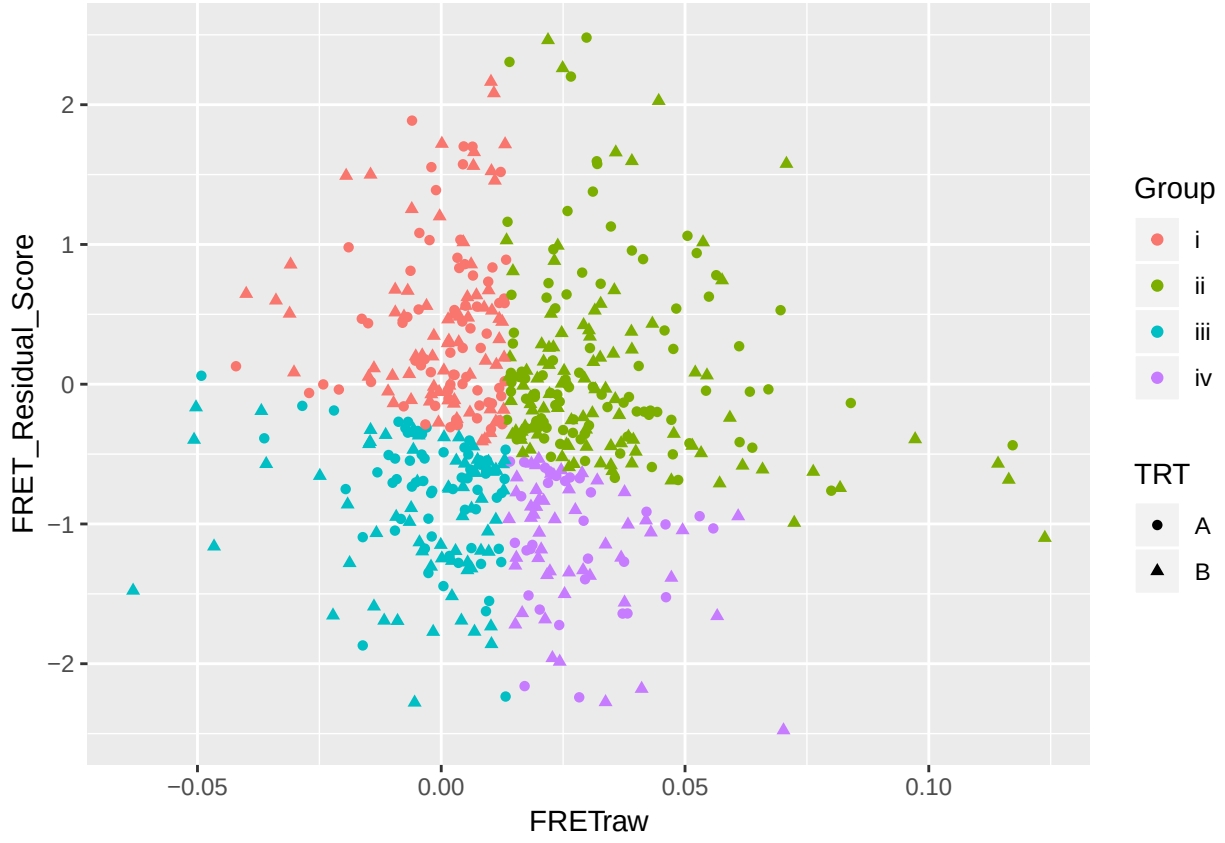
```
# Cut data and name change
data$FRETraw <- data$FRET
breaks <- quantile(data$FRETraw, probs = c(0.0, 0.5, 1.0), na.rm = T)
data$FRET <- cut(data$FRETraw, breaks = breaks, labels = c("low", "high"), include.lowest = T)
```

Group patients according to FRET and predicted class

```
data$Group <- ifelse(data$FRET == "low",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

Plot FRET vs residual signature

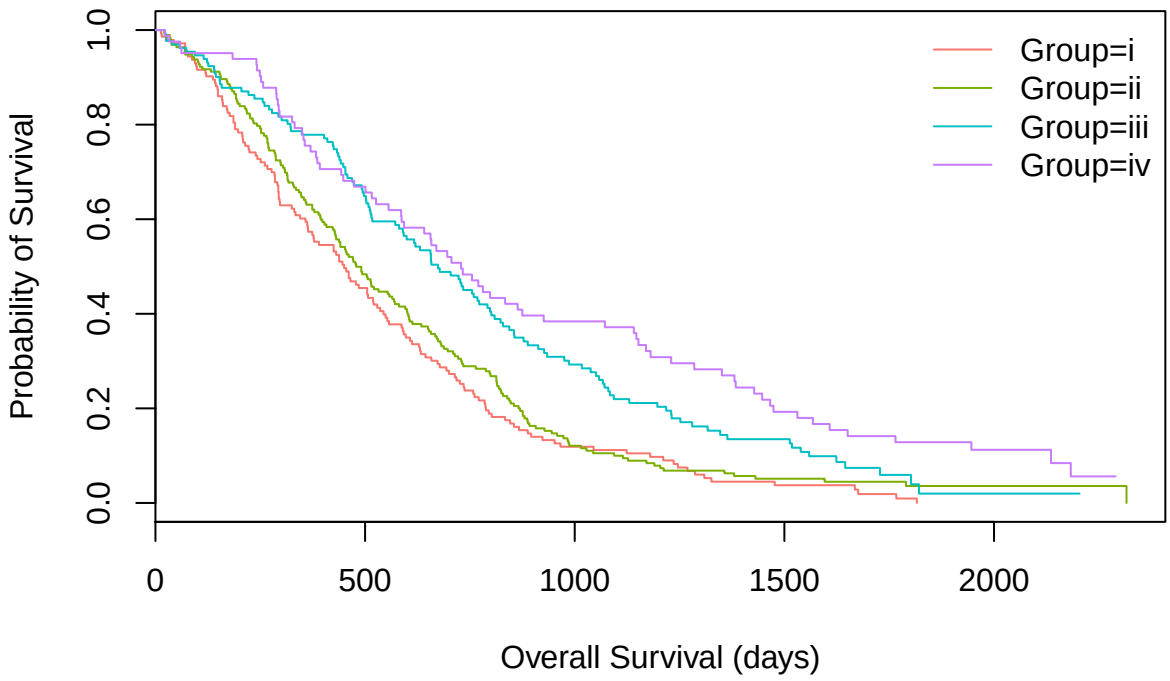
```
data <- subset(data, FRET_Residual_Score<10)   # one outlier: really high residual score

ggplot(data, aes(FRETraw, FRET_Residual_Score)) +
  geom_point(aes(color = Group, shape = TRT))
```



Plot survival curves for the groups

```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)
```

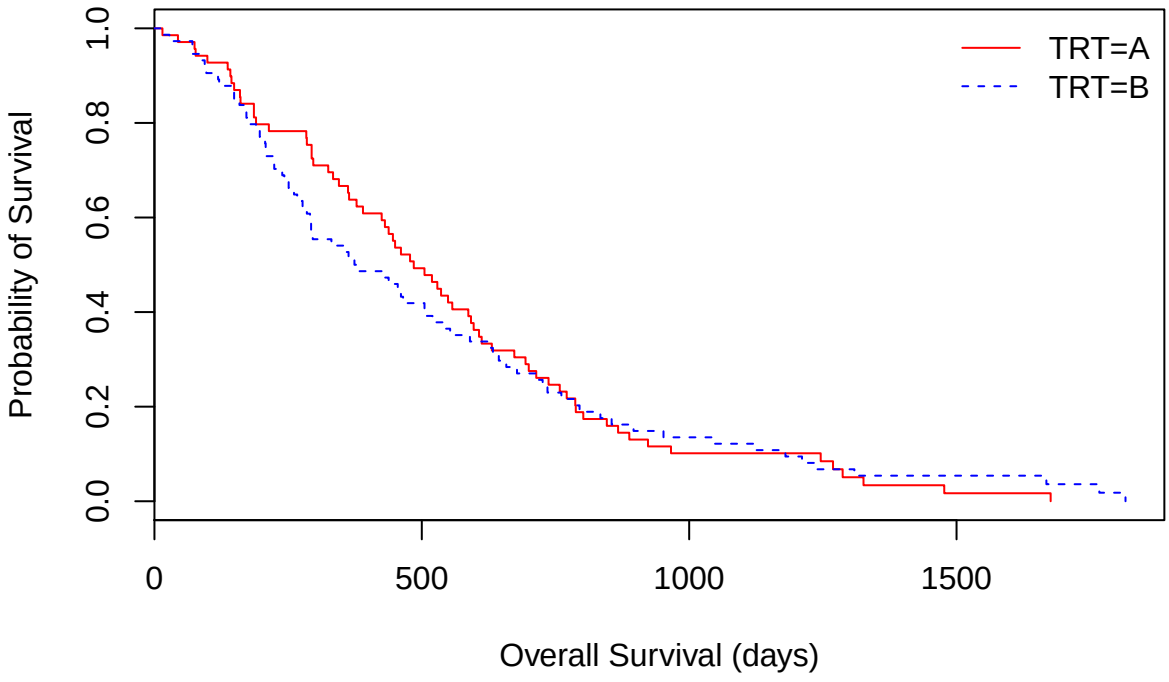
```r
km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```r
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##              n events median 0.95LCL 0.95UCL
## Group=i    143    141    450     364     536
## Group=ii   193    184    479     430     571
## Group=iii  131    120    674     590     798
## Group=iv    82     73    729     587    1072
```

```r
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



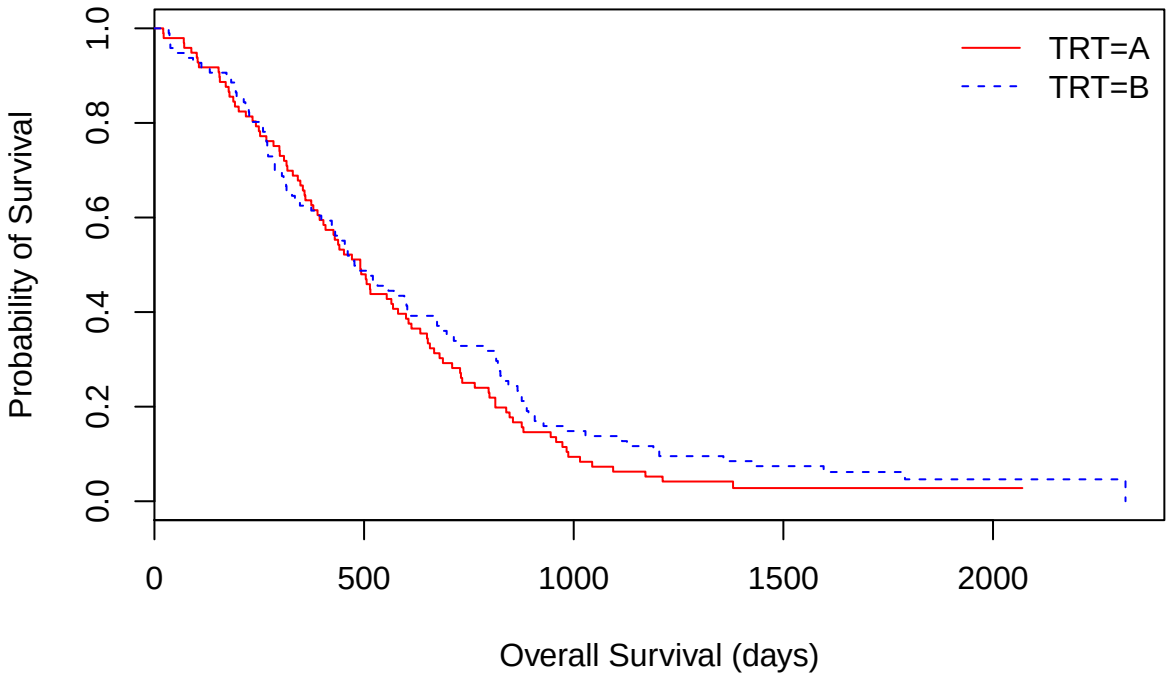

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A 69     68    485     425     597
## TRT=B 74     73    376     291     544
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 69       68     69.3    0.0230    0.0462
## TRT=B 74       73     71.7    0.0222    0.0462
##
##  Chisq= 0  on 1 degrees of freedom, p= 0.8
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



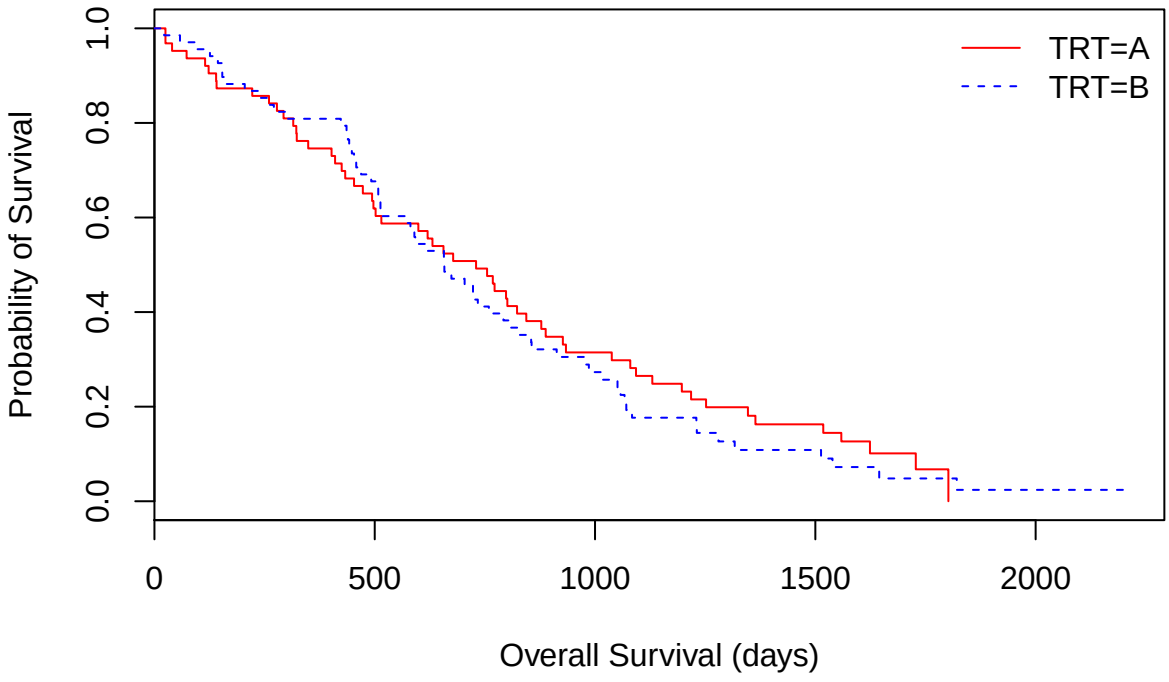

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 97     93    491     403     600
## TRT=B 96     91    477     423     671
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 97       93     85.8     0.608      1.16
## TRT=B 96       91     98.2     0.531      1.16
##
##  Chisq= 1.2  on 1 degrees of freedom, p= 0.3
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



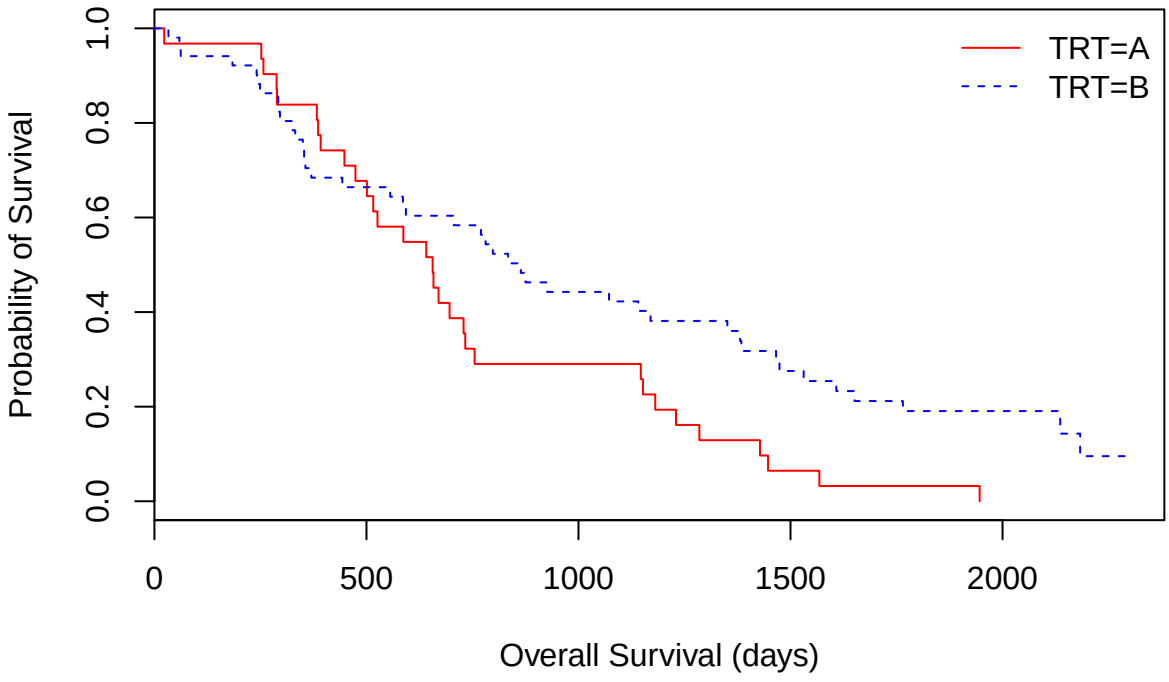

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 63     57    730     502     888
## TRT=B 68     63    658     517     829
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 63       57     60.2     0.174     0.356
## TRT=B 68       63     59.8     0.175     0.356
##
##  Chisq= 0.4  on 1 degrees of freedom, p= 0.6
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A 31     31    656     501    1147
## TRT=B 51     42    864     593    1384
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 31       31     21.9      3.77      5.71
## TRT=B 51       42     51.1      1.62      5.71
##
##  Chisq= 5.7  on 1 degrees of freedom, p= 0.02
```

Investigate SUMLES vs its Residual Score

Get fresh data set of FRET patients

```
data <- subset(patient_data, FRET.cohort!=0)
```

Classifiy FRET patients according to SUMLES

```
data$SUMLESraw <- data$SUMLES
breaks <- quantile(data$SUMLESraw, probs = c(0.0, 0.5, 1.0), na.rm = T)
data$SUMLES <- cut(data$SUMLESraw, breaks = breaks, labels = c("low", "high"), include.lowest = T)
```

Group patients according to SUMLES and predicted class

```
data$Group <- ifelse(data$SUMLES == "low",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

Plot SUMLES vs residual signature

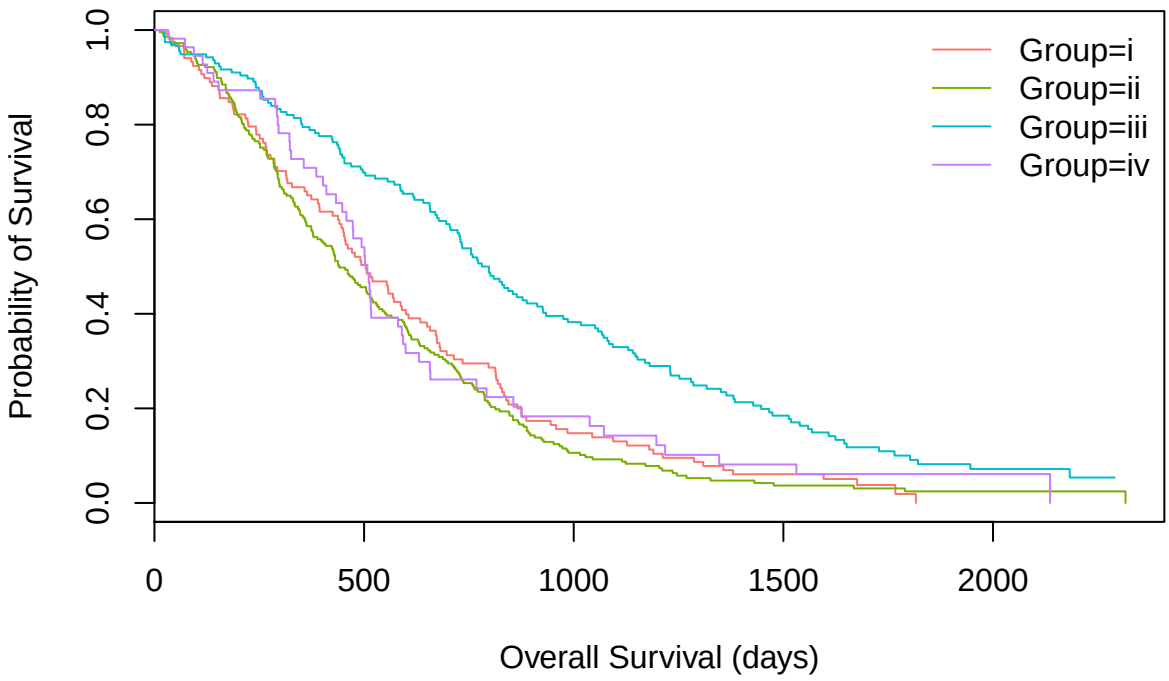
```
data <- subset(data, SUMLES_Residual_Score<8)   # one outlier: really high residual score

ggplot(data, aes(SUMLESraw, SUMLES_Residual_Score)) +
  geom_point(aes(color = Group, shape = TRT))
```

```
## Warning: Removed 3 rows containing missing values (geom_point).
```

Plot survival curves for the groups

```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)
```

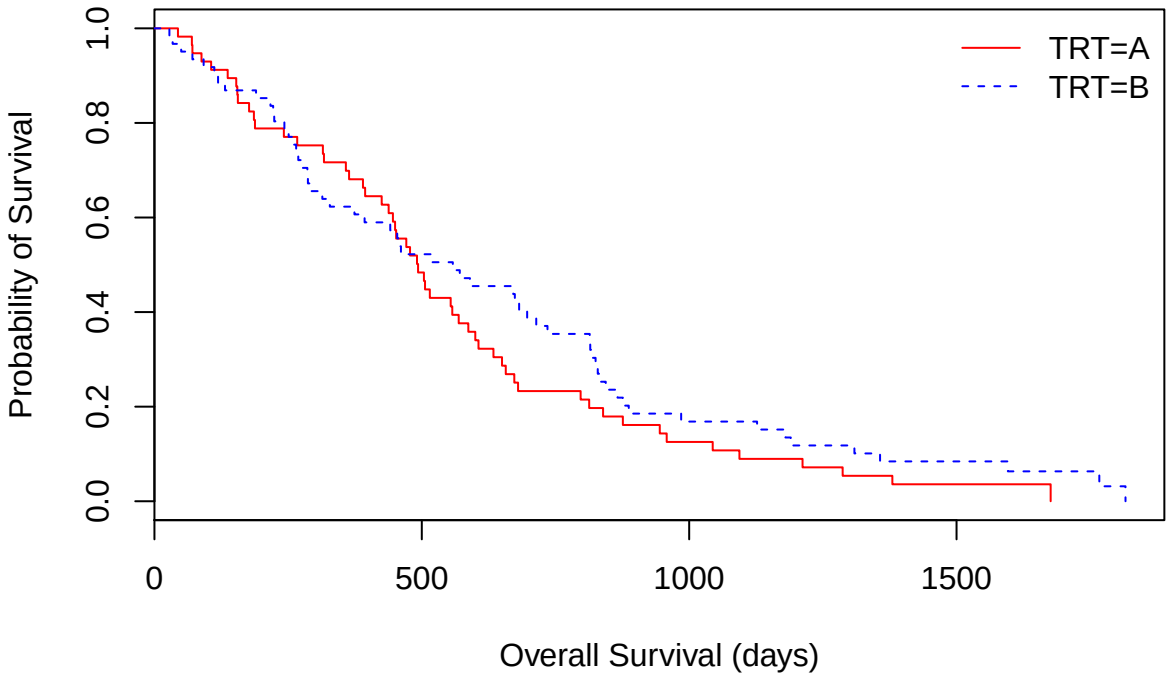
```r
km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```r
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##    3 observations deleted due to missingness
##             n events median 0.95LCL 0.95UCL
## Group=i   118    113    504     446     600
## Group=ii  217    211    441     379     519
## Group=iii 156    140    790     723     926
## Group=iv   55     51    508     448     593
```

```r
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



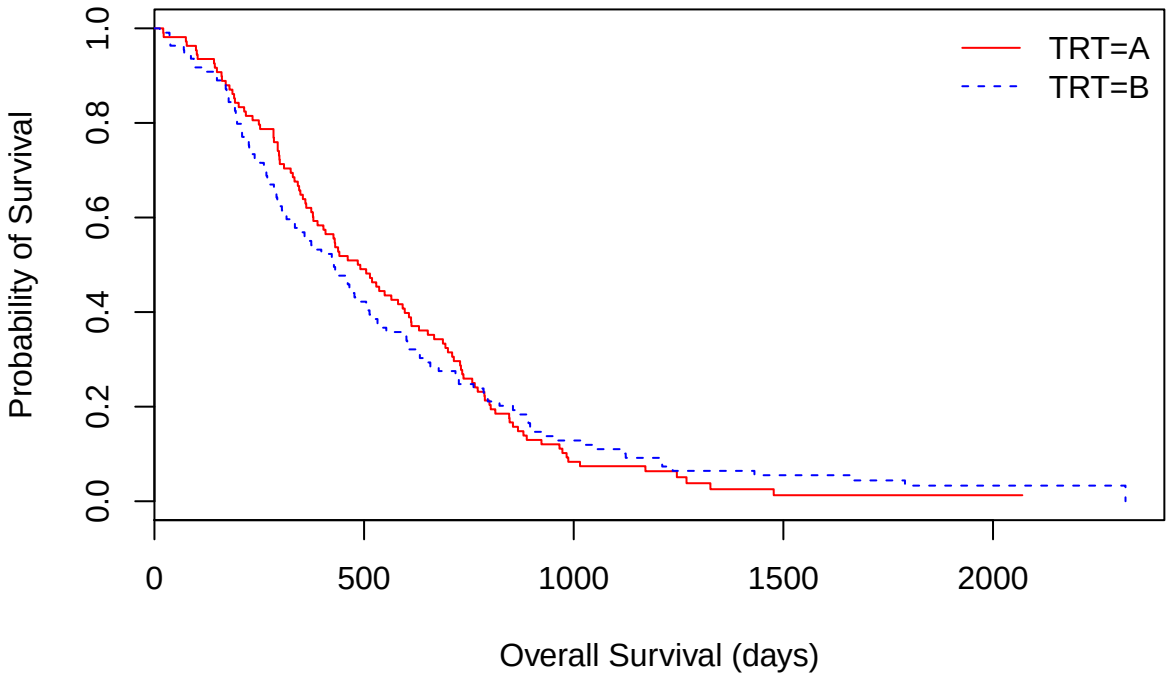

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 57     55    493     438     600
## TRT=B 61     58    558     374     735
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 57       55       49     0.732      1.33
## TRT=B 61       58       64     0.560      1.33
##
##  Chisq= 1.3  on 1 degrees of freedom, p= 0.2
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



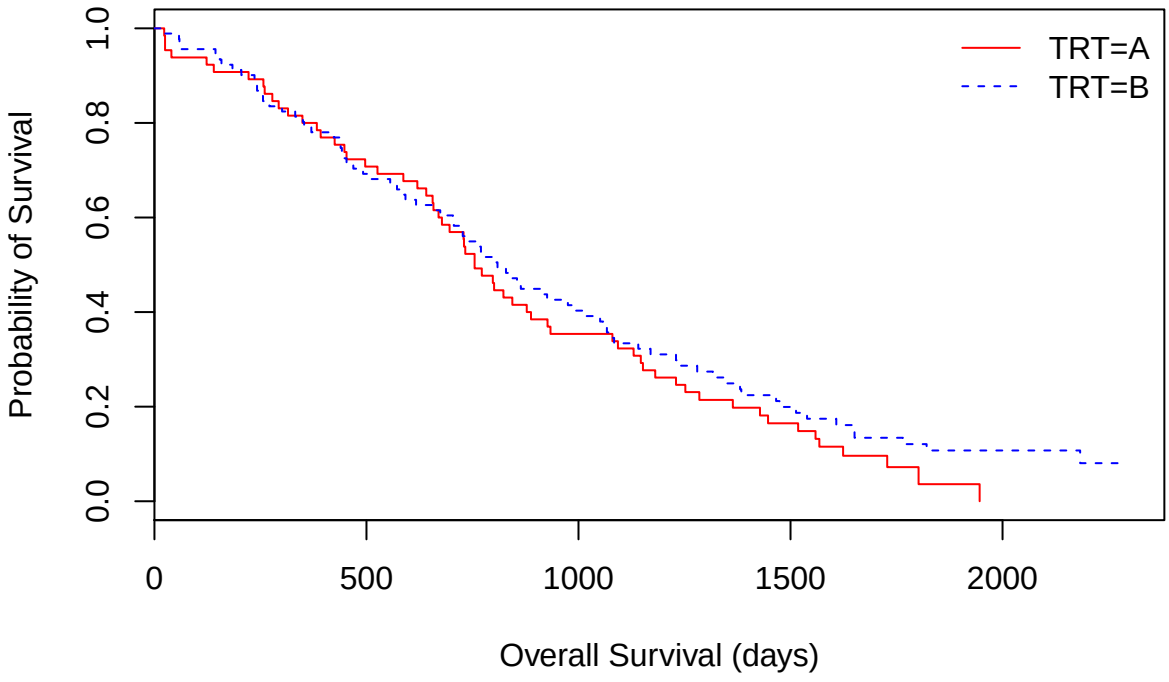

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 108    105    488     389     607
## TRT=B 109    106    428     335     513
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 108      105      105   0.00143   0.00291
## TRT=B 109      106      106   0.00143   0.00291
##
##  Chisq= 0  on 1 degrees of freedom, p= 1
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



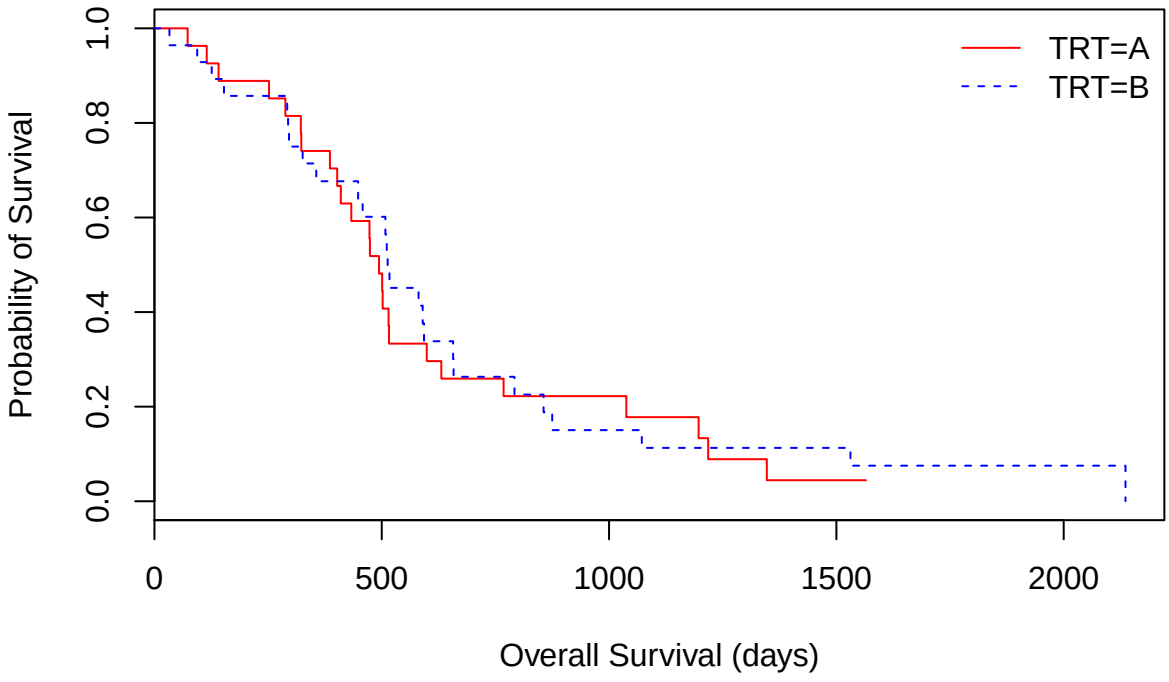

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 65     61    755     670     934
## TRT=B 91     79    809     706    1051
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 65       61     55.2     0.611      1.03
## TRT=B 91       79     84.8     0.398      1.03
##
##  Chisq= 1  on 1 degrees of freedom, p= 0.3
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 27     25    494     410     631
## TRT=B 28     26    513     448     658
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 27       25     23.7    0.0678      0.13
## TRT=B 28       26     27.3    0.0590      0.13
##
##  Chisq= 0.1  on 1 degrees of freedom, p= 0.7
```

Investigate WBC vs its Residual Score

Get fresh data set of FRET patients

```
data <- subset(patient_data, FRET.cohort!=0)
```

Classifiy FRET patients according to WBC

```
data$WBCraw <- data$WBC
breaks <- quantile(data$WBCraw, probs = c(0.0, 0.5, 1.0), na.rm = T)
data$WBC <- cut(data$WBCraw, breaks = breaks, labels = c("low", "high"), include.lowest = T)
```

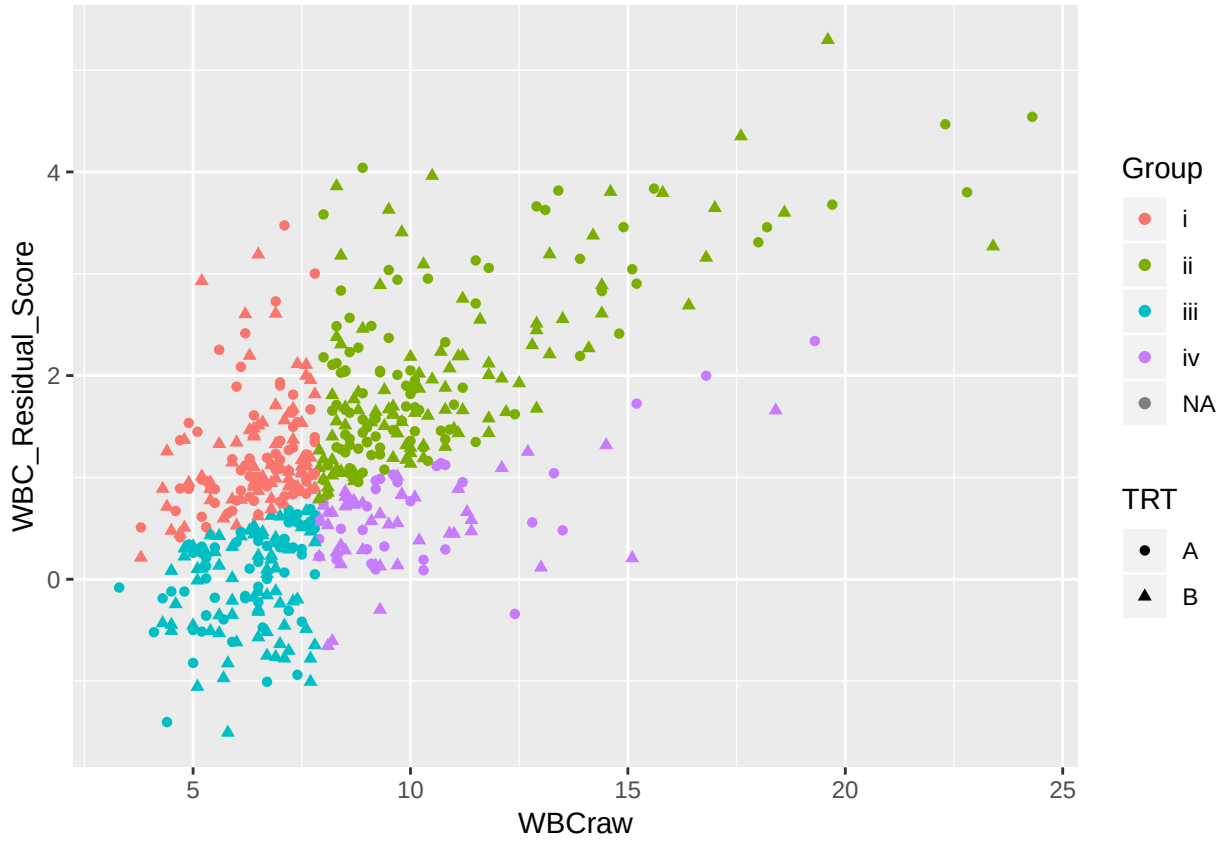
Group patients according to WBC and predicted class

```
data$Group <- ifelse(data$WBC == "low",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

Plot WBC vs residual signature

```
data <- subset(data, WBC_Residual_Score<8)   # one outlier: really high residual score

ggplot(data, aes(WBCraw, WBC_Residual_Score)) +
  geom_point(aes(color = Group, shape = TRT))
```

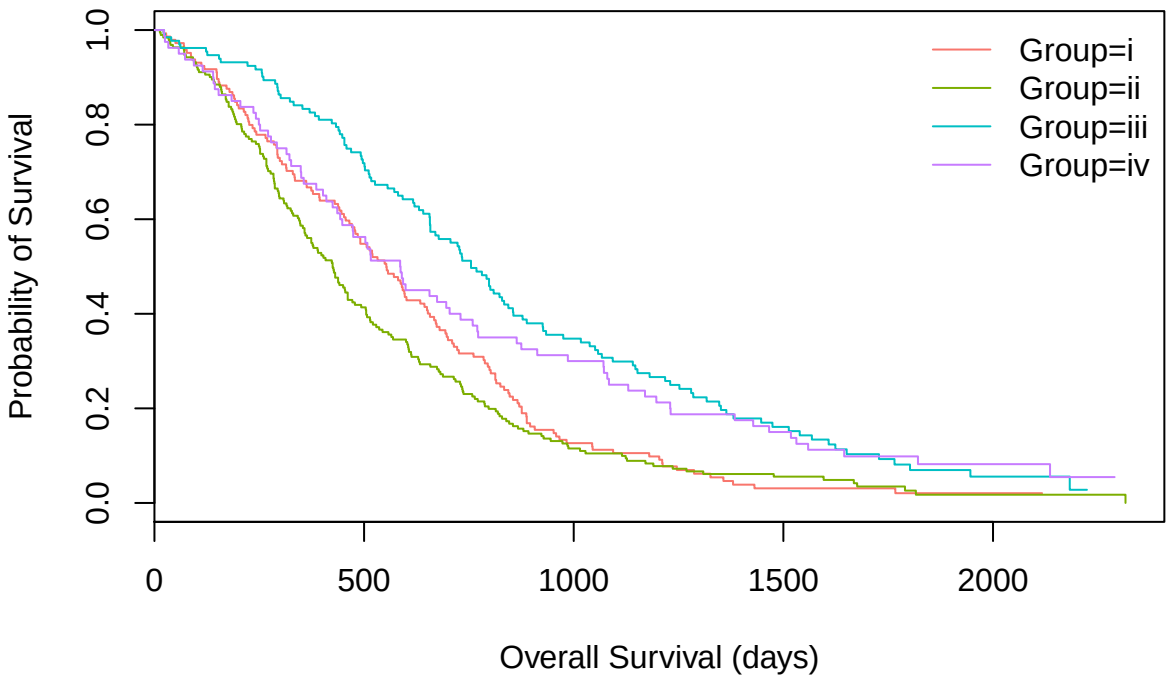
```
## Warning: Removed 1 rows containing missing values (geom_point).
```



Plot survival curves for the groups

```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)
```

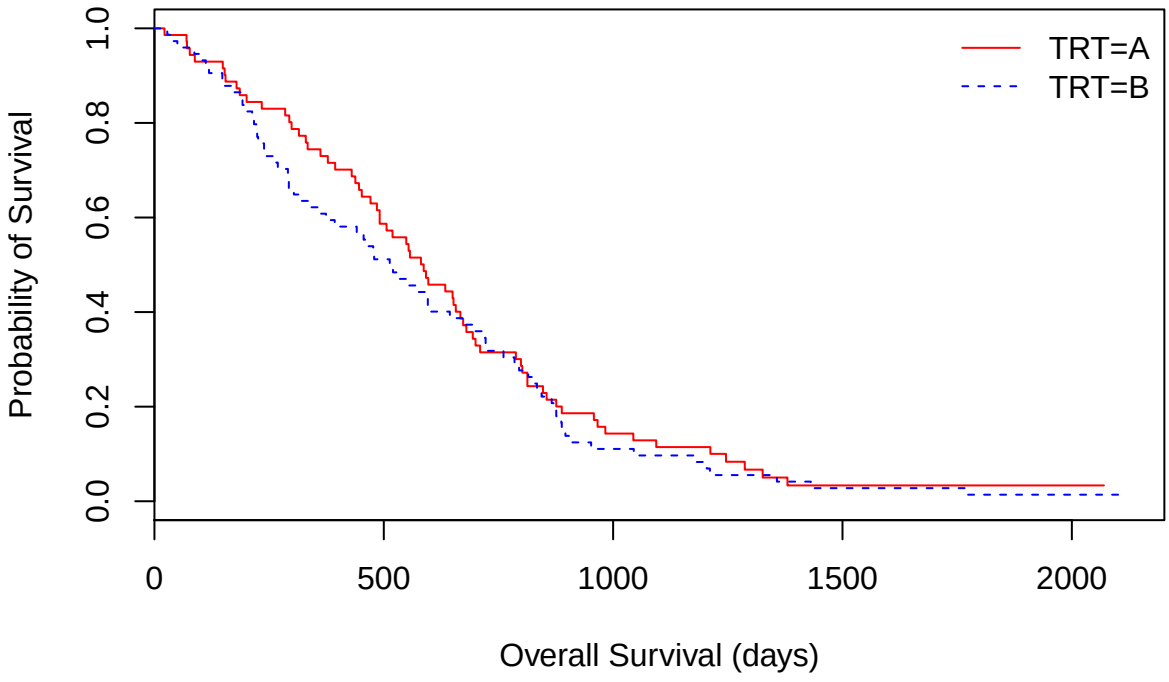
```
km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##    1 observation deleted due to missingness
##              n events median 0.95LCL 0.95UCL
## Group=i    145    139    553     479     650
## Group=ii   191    186    425     360     478
## Group=iii  132    118    755     658     855
## Group=iv    80     74    586     448     759
```

```
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



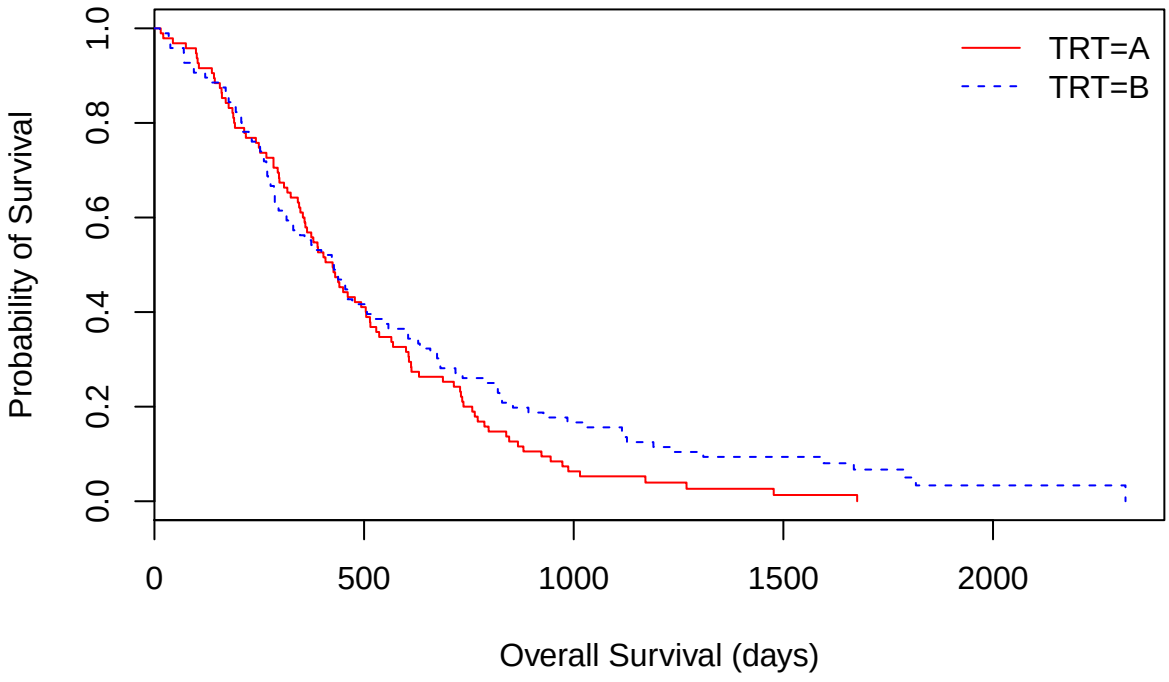

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 71     67    587     491     680
## TRT=B 74     72    513     374     697
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 71       67     71.6     0.291     0.605
## TRT=B 74       72     67.4     0.309     0.605
##
##  Chisq= 0.6  on 1 degrees of freedom, p= 0.4
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



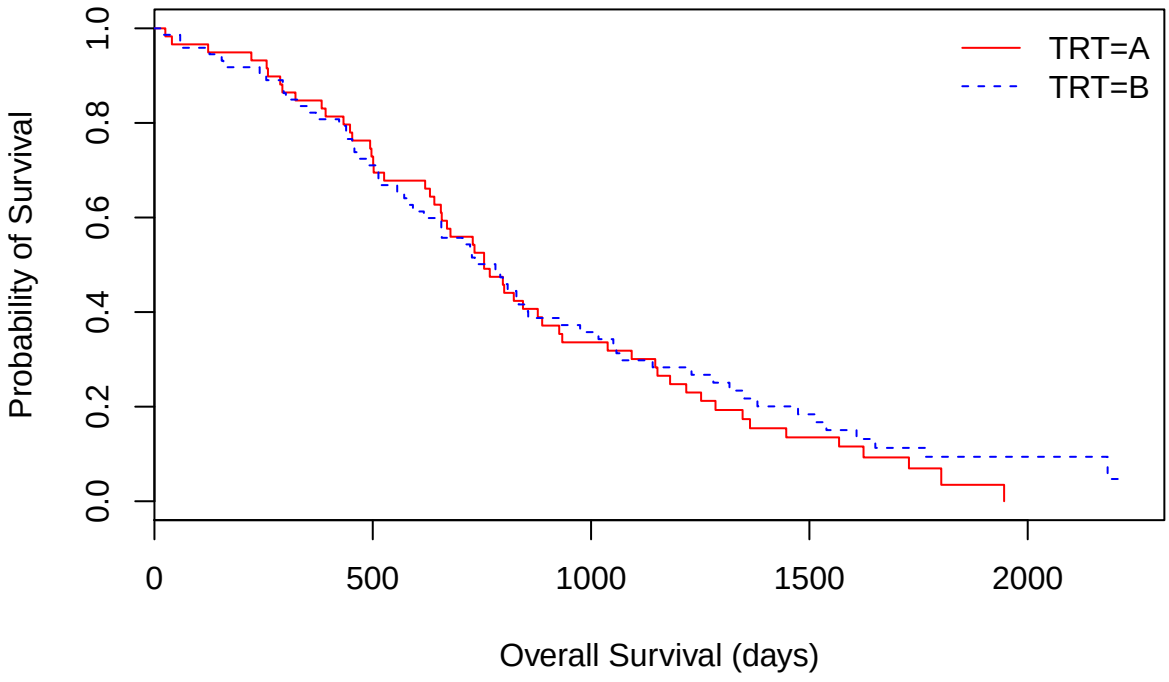

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 95     94    425     358     514
## TRT=B 96     92    426     328     521
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 95       94     83.9      1.23      2.33
## TRT=B 96       92    102.1      1.01      2.33
##
##  Chisq= 2.3  on 1 degrees of freedom, p= 0.1
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



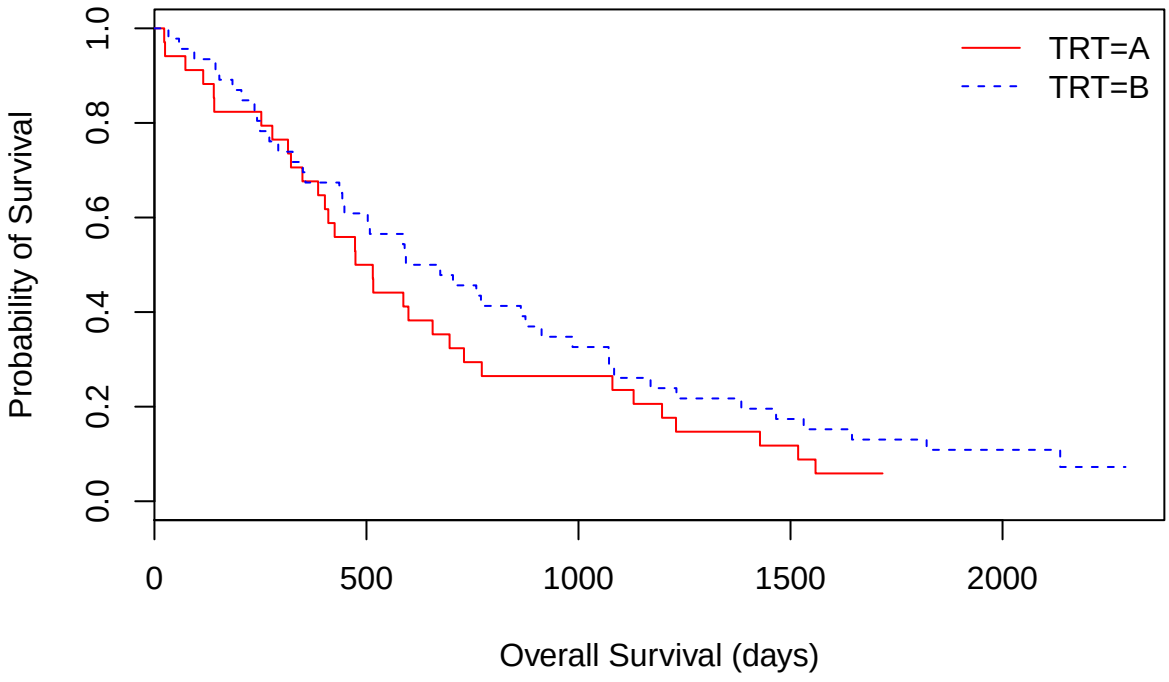

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 59     55    755     656     934
## TRT=B 73     63    781     617     975
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 59       55     51.7     0.207     0.374
## TRT=B 73       63     66.3     0.162     0.374
##
##  Chisq= 0.4  on 1 degrees of freedom, p= 0.5
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 34     32    494     402     730
## TRT=B 46     42    634     448     986
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 34       32     27.4     0.788      1.28
## TRT=B 46       42     46.6     0.462      1.28
##
##  Chisq= 1.3  on 1 degrees of freedom, p= 0.3
```

Investigate NEUT vs its Residual Score

Get fresh data set of FRET patients

```
data <- subset(patient_data, FRET.cohort!=0)
```

Classifiy FRET patients according to NEUT

```
data$NEUTraw <- data$NEUT
breaks <- quantile(data$NEUTraw, probs = c(0.0, 0.5, 1.0), na.rm = T)
data$NEUT <- cut(data$NEUTraw, breaks = breaks, labels = c("low", "high"), include.lowest = T)
```

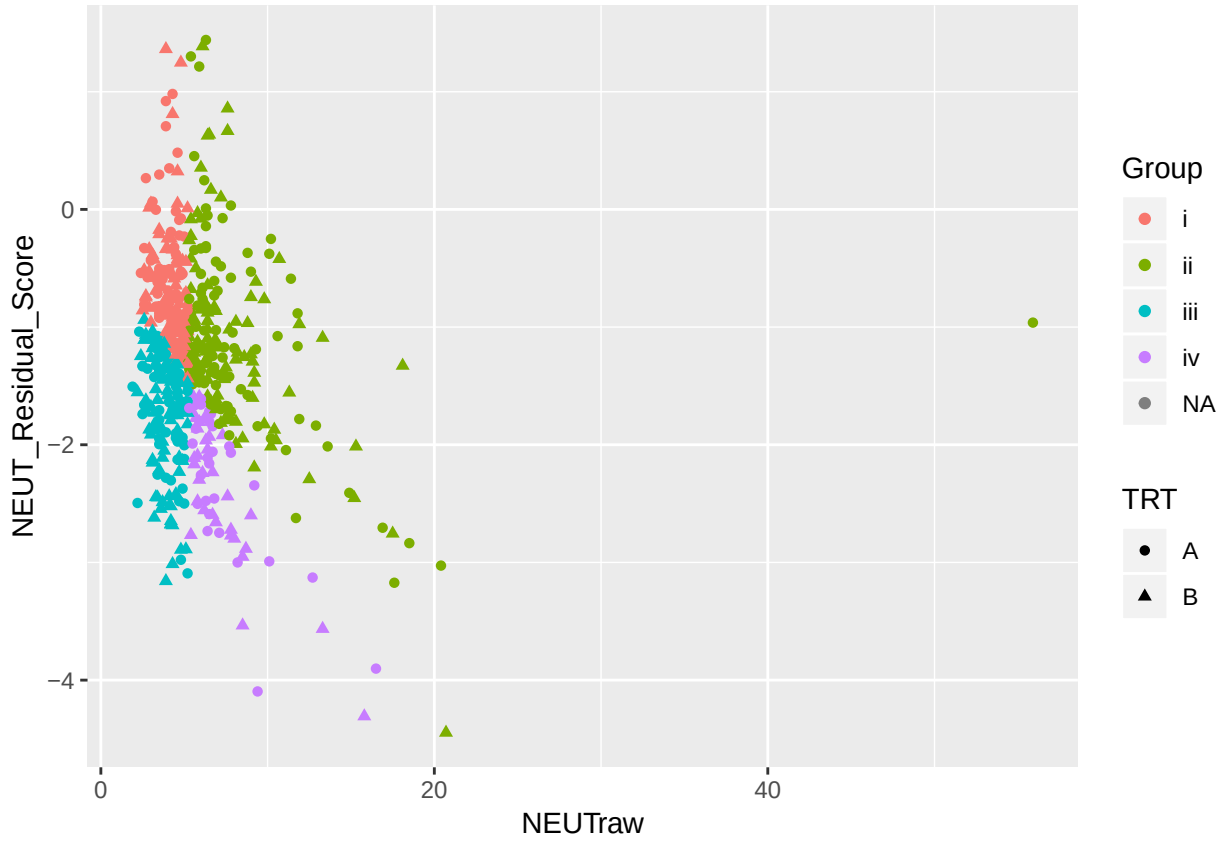
Group patients according to NEUT and predicted class

```
data$Group <- ifelse(data$NEUT == "low",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

Plot NEUT vs residual signature

```
#data <- subset(data, NEUT_Residual_Score<8)   # one outlier: really high residual score

ggplot(data, aes(NEUTraw, NEUT_Residual_Score)) +
  geom_point(aes(color = Group, shape = TRT))
```

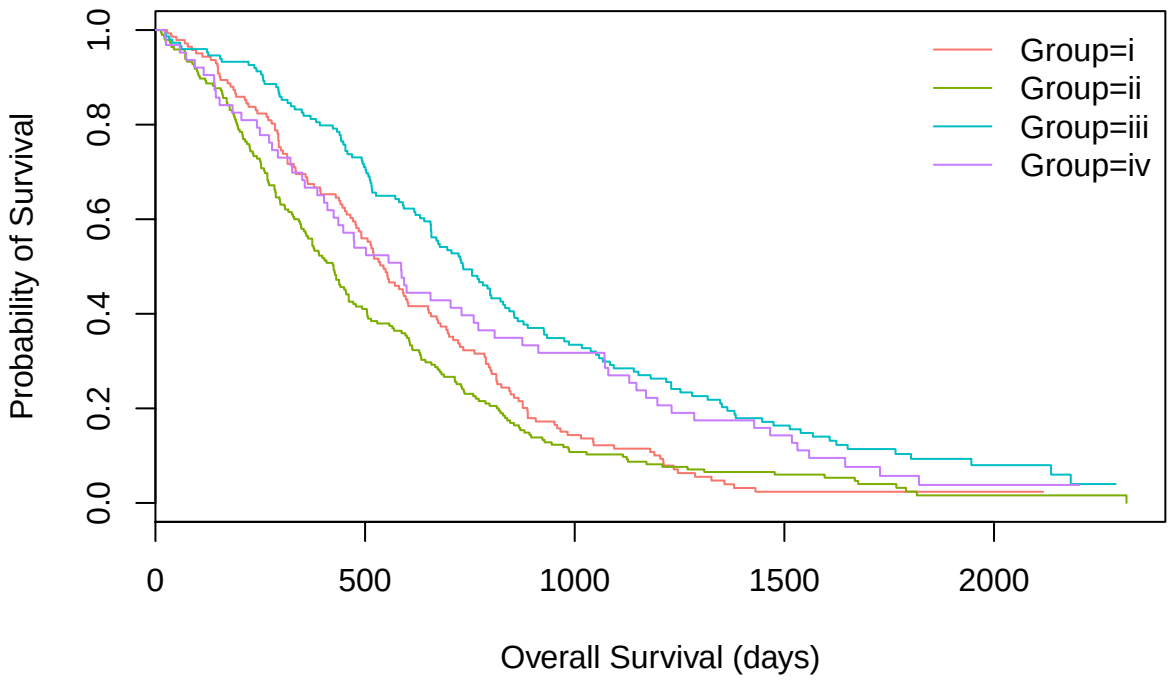
```
## Warning: Removed 1 rows containing missing values (geom_point).
```



Plot survival curves for the groups

```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)
```

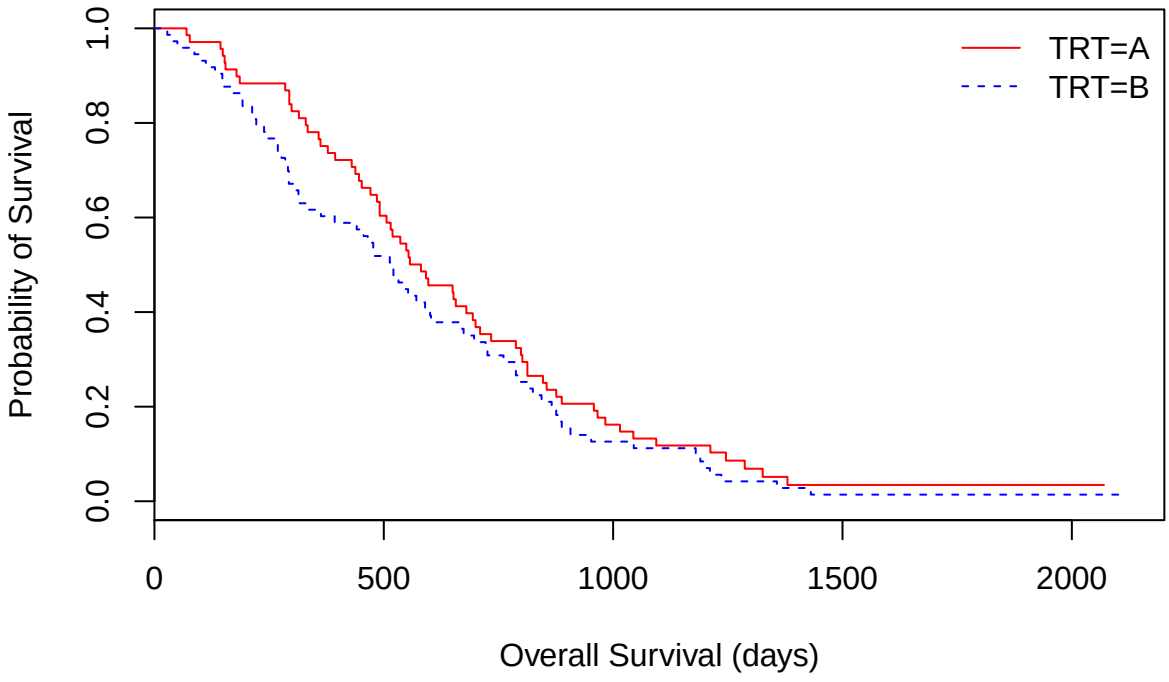
```
km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##    1 observation deleted due to missingness
##             n events median 0.95LCL 0.95UCL
## Group=i   142    136    544     485     650
## Group=ii  195    190    425     360     472
## Group=iii 149    132    734     658     834
## Group=iv   63     60    586     425     809
```

```
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



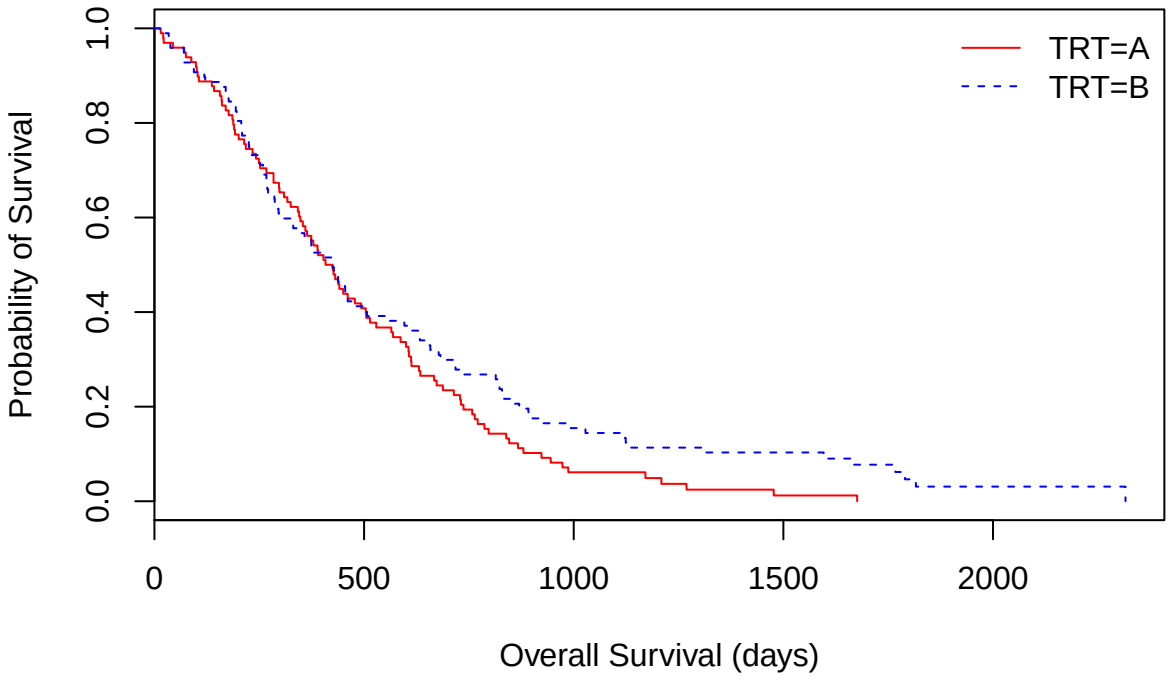

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 69     65    581     491     710
## TRT=B 73     71    520     393     671
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 69       65     72.1     0.699       1.5
## TRT=B 73       71     63.9     0.789       1.5
##
##  Chisq= 1.5  on 1 degrees of freedom, p= 0.2
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



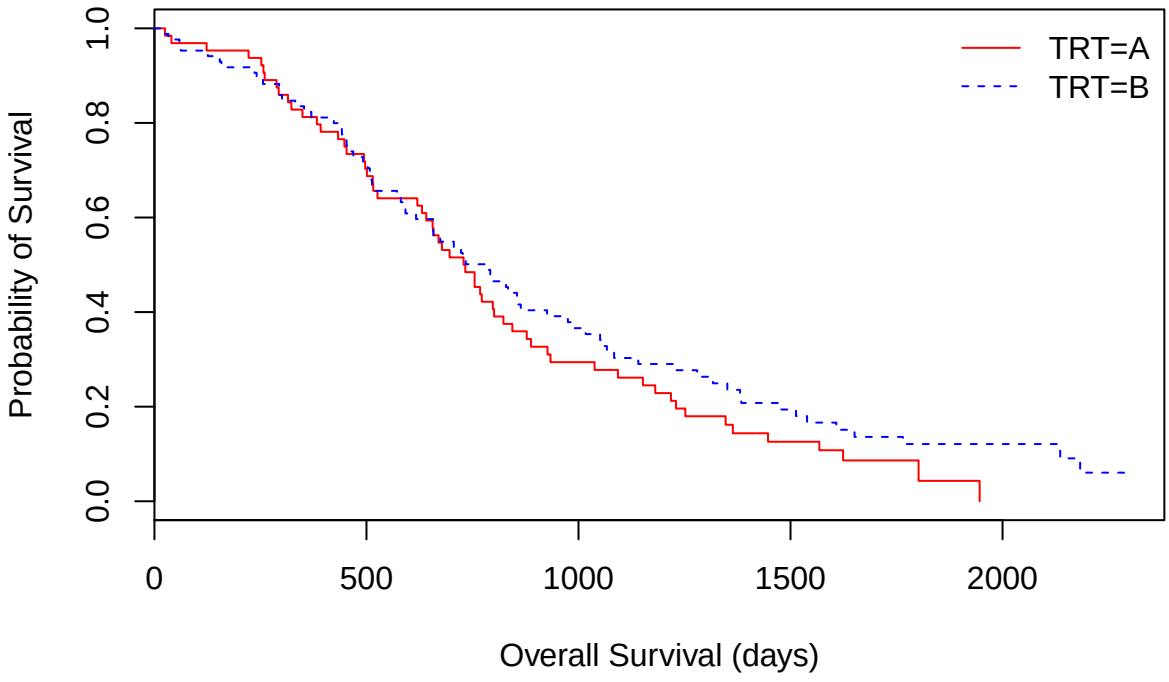

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A 98     97    416     354     505
## TRT=B 97     93    425     328     558
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 98       97     85.6      1.52      2.89
## TRT=B 97       93    104.4      1.24      2.89
##
##  Chisq= 2.9  on 1 degrees of freedom, p= 0.09
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



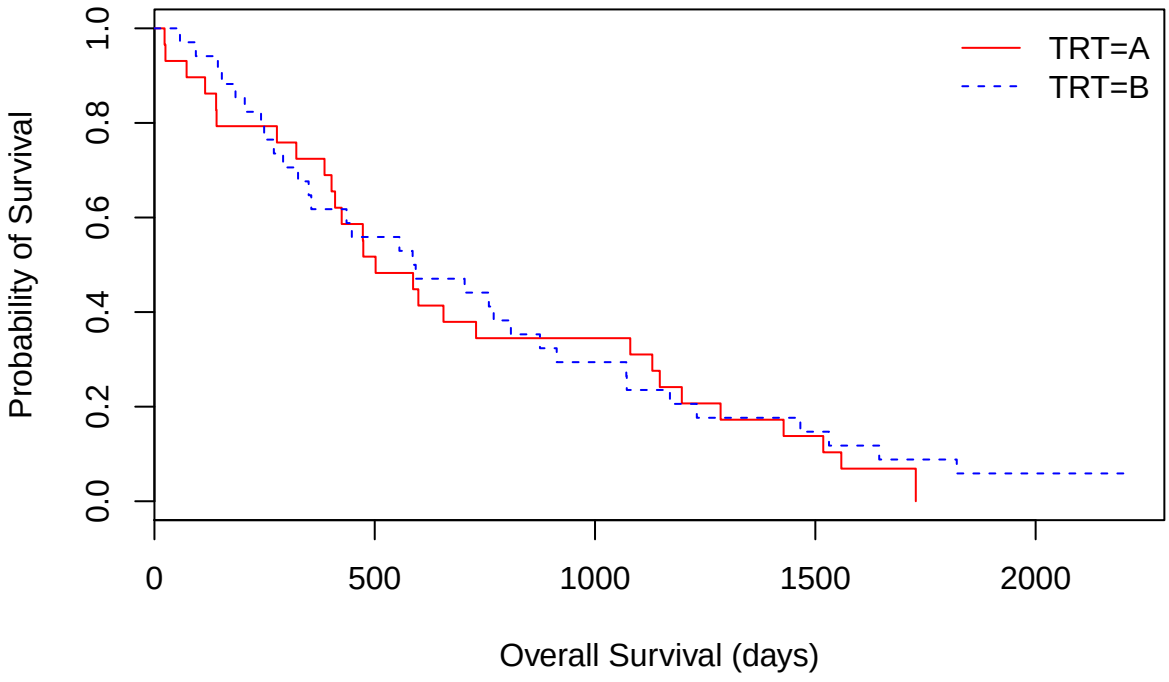

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 64     59    731     641     844
## TRT=B 85     73    781     657     975
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 64       59     52.5     0.810      1.37
## TRT=B 85       73     79.5     0.535      1.37
##
##  Chisq= 1.4  on 1 degrees of freedom, p= 0.2
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 29     28    502     410    1130
## TRT=B 34     32    590     356     913
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 29       28     26.4    0.0909     0.167
## TRT=B 34       32     33.6    0.0717     0.167
##
##  Chisq= 0.2  on 1 degrees of freedom, p= 0.7
```

Investigate SHB0 vs its Residual Score

Get fresh data set of FRET patients

```
data <- subset(patient_data, FRET.cohort!=0)
```

Classifiy FRET patients according to SHB0

```
data$SHB0raw <- data$SHB0
data$SHB0 <- ifelse(data$SHB0raw > 0, "high", "low")
```

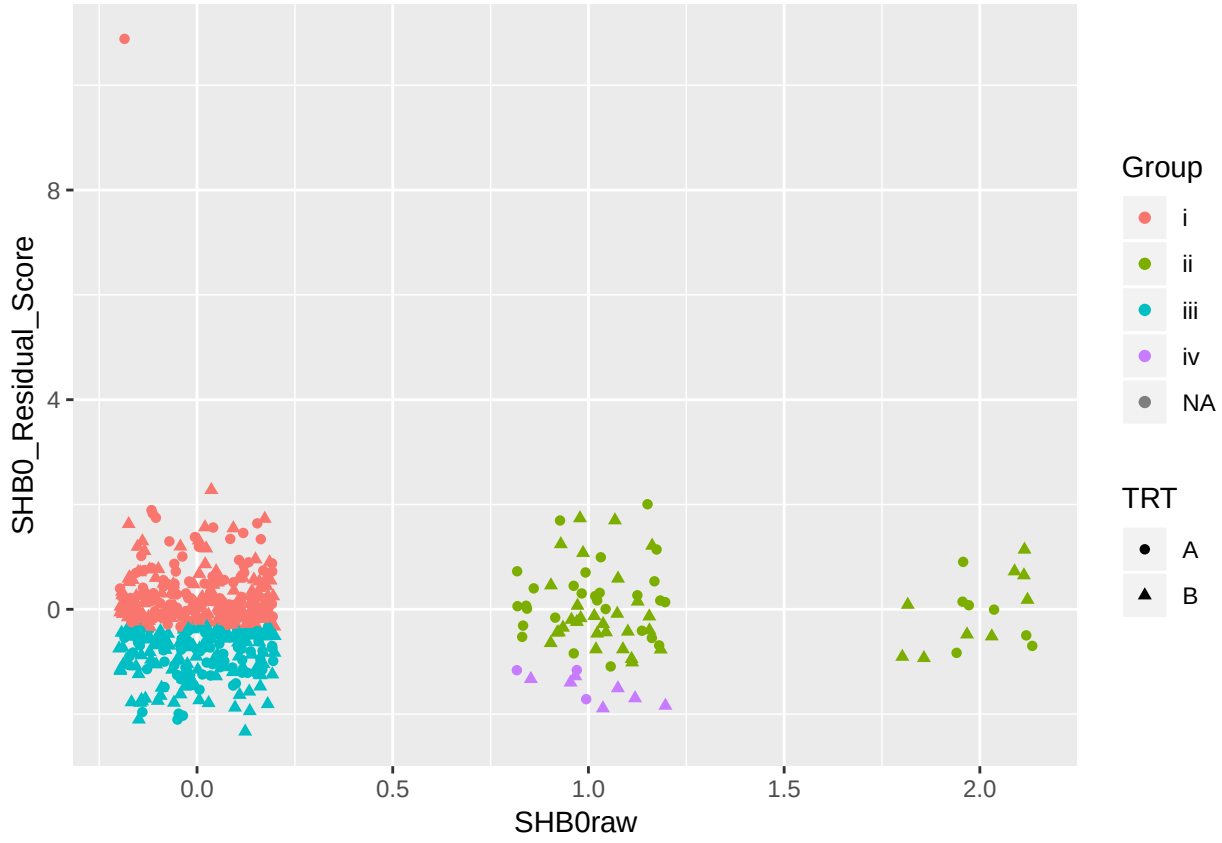
Group patients according to SHB0 and predicted class

```
data$Group <- ifelse(data$SHB0 == "low",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

Plot SHB0 vs residual signature

```
#data <- subset(data, SHB0_Residual_Score<8)   # one outlier: really high residual score

ggplot(data, aes(SHB0raw, SHB0_Residual_Score)) +
  geom_jitter(width=0.2, aes(color = Group, shape = TRT))
```

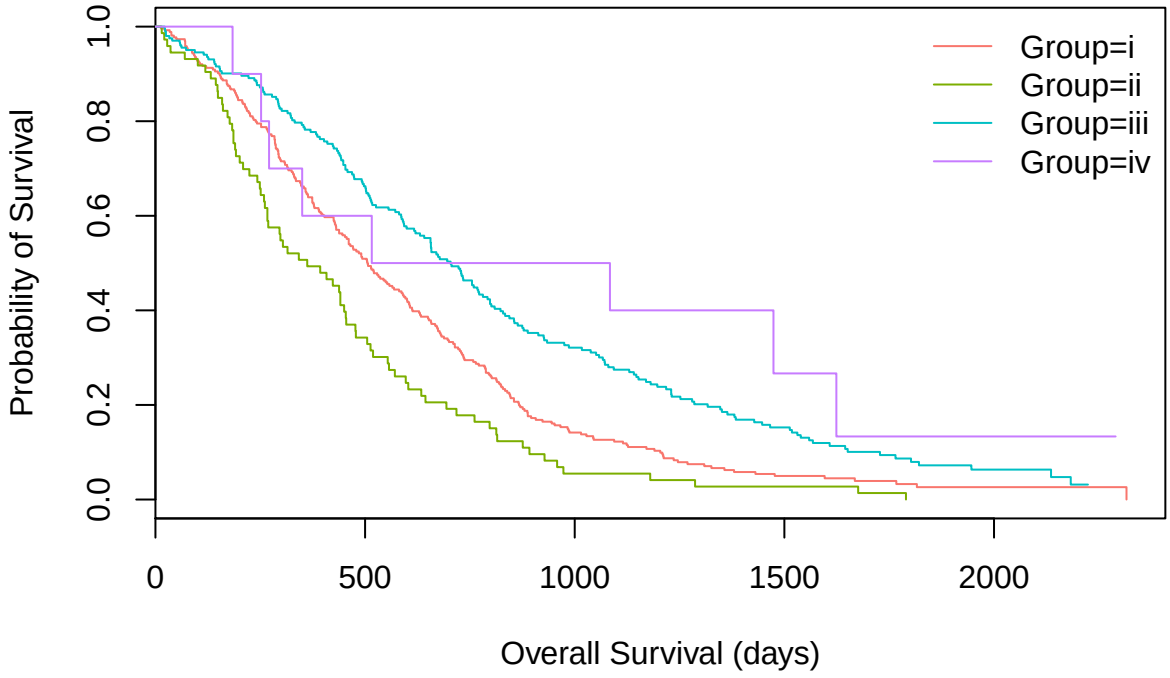
```
## Warning: Removed 1 rows containing missing values (geom_point).
```



Plot survival curves for the groups

```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)
```

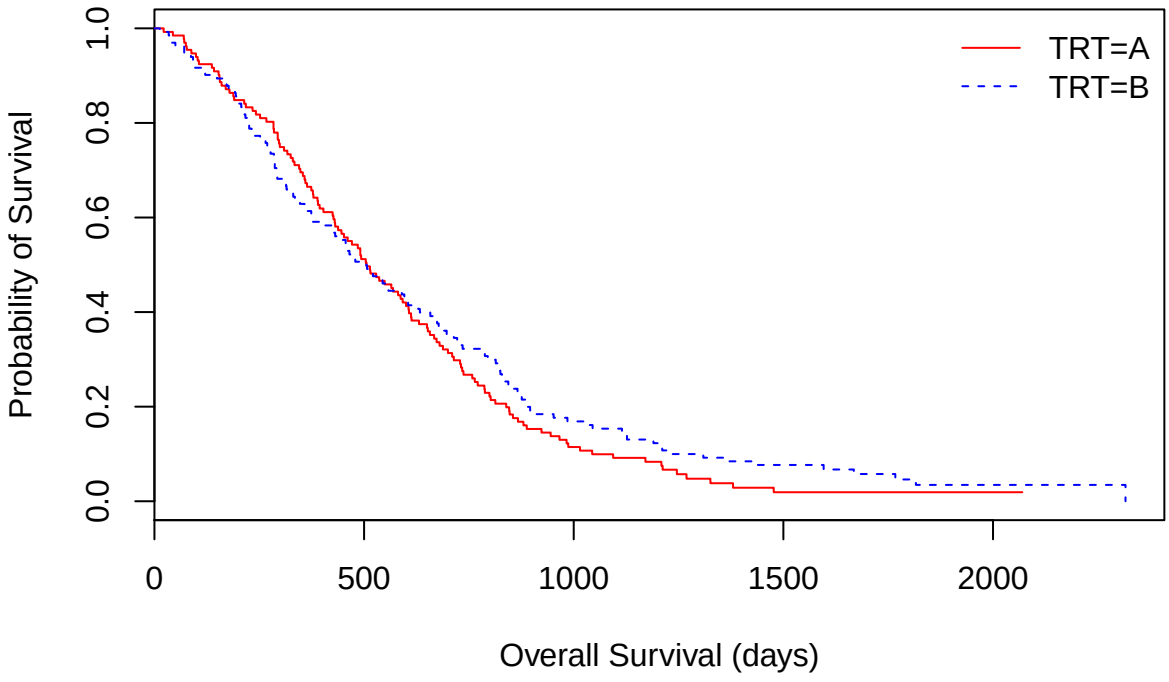
```r
km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```r
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##    1 observation deleted due to missingness
##             n events median 0.95LCL 0.95UCL
## Group=i   264    253    506     452     590
## Group=ii   73     73    362     267     455
## Group=iii 202    184    704     620     792
## Group=iv   10      8    800     271      NA
```

```r
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



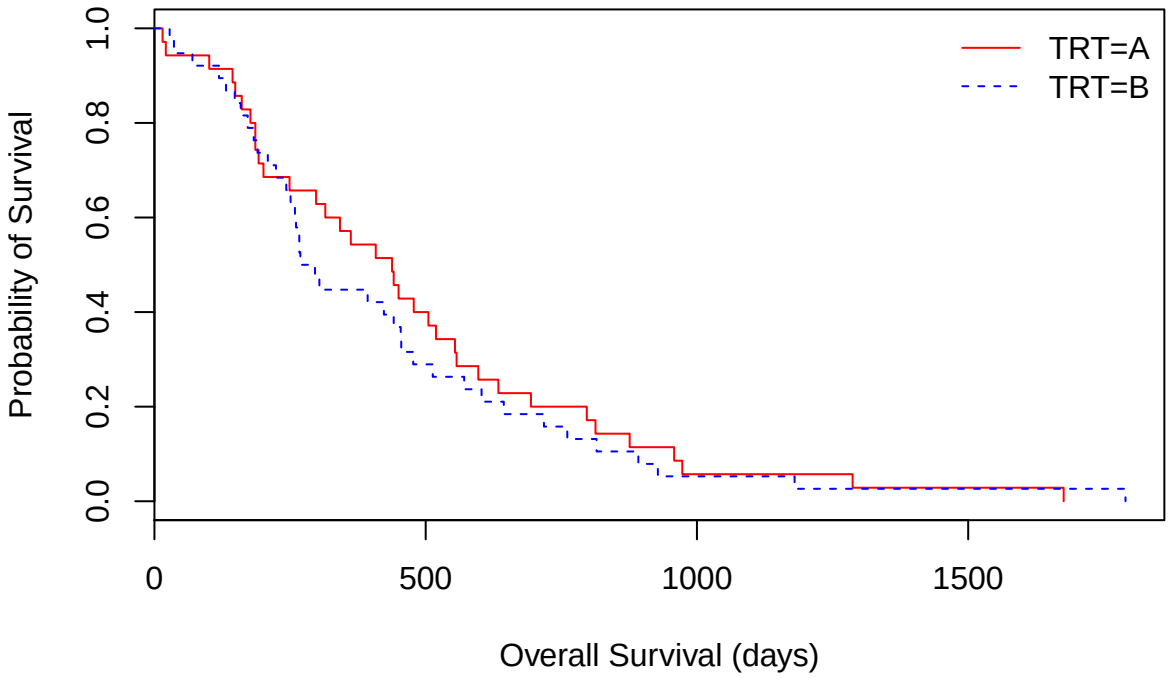

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 132    127    506     438     606
## TRT=B 132    126    505     425     633
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 132      127      119     0.513     0.993
## TRT=B 132      126      134     0.457     0.993
##
##  Chisq= 1  on 1 degrees of freedom, p= 0.3
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



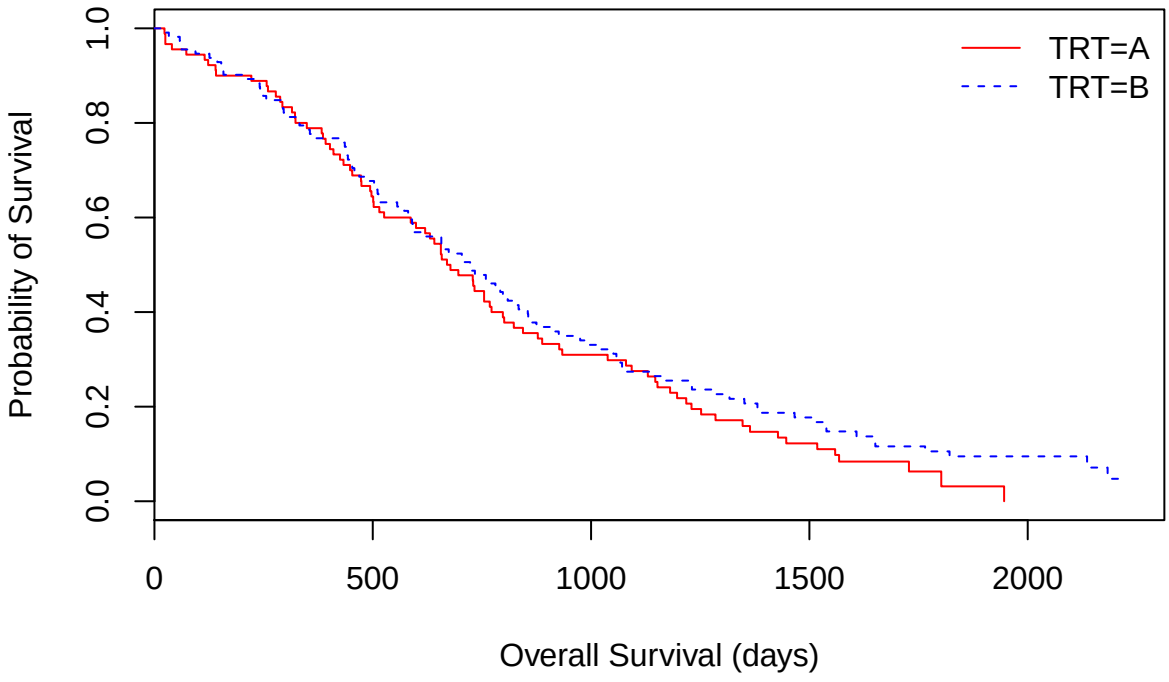

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A 35     35    438     298     557
## TRT=B 38     38    282     251     477
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 35       35     37.3     0.148     0.309
## TRT=B 38       38     35.7     0.155     0.309
##
##  Chisq= 0.3  on 1 degrees of freedom, p= 0.6
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



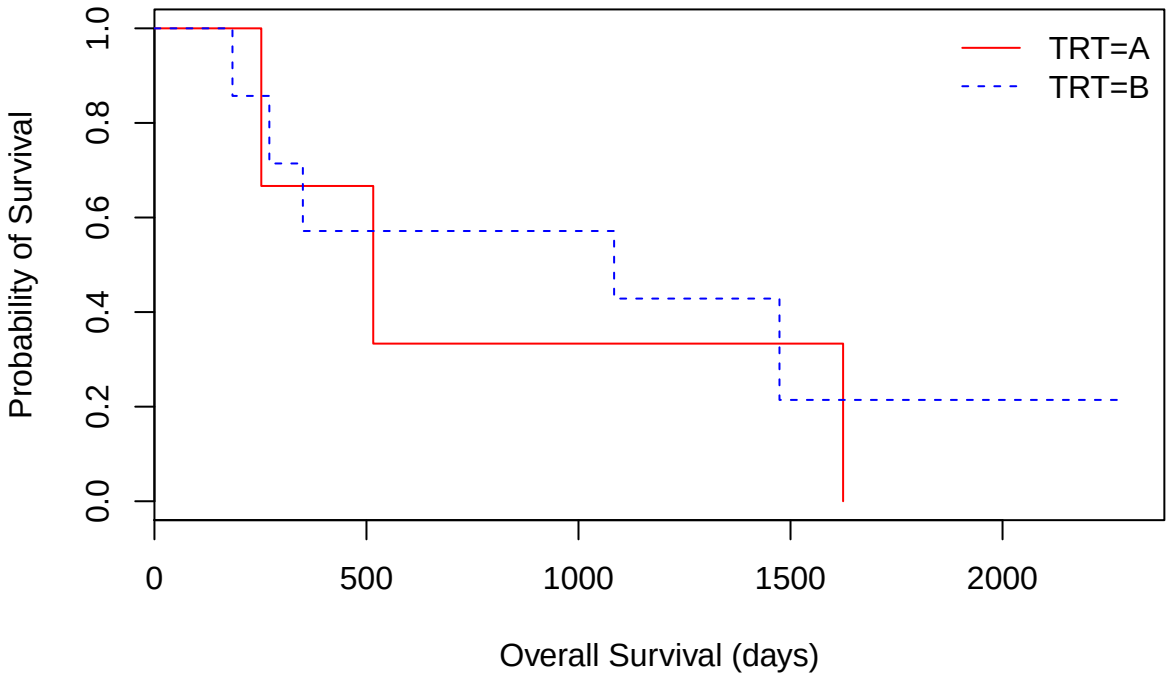

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A  90     84    674     587     801
## TRT=B 112    100    723     592     855
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A  90       84     76.8     0.681      1.19
## TRT=B 112      100    107.2     0.487      1.19
##
##  Chisq= 1.2  on 1 degrees of freedom, p= 0.3
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##       n events median 0.95LCL 0.95UCL
## TRT=A 3      3    516     252      NA
## TRT=B 7      5   1084     271      NA
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##       N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 3        3     2.54    0.0850     0.128
## TRT=B 7        5     5.46    0.0394     0.128
##
##  Chisq= 0.1  on 1 degrees of freedom, p= 0.7
```

Investigate mlivonly vs its Residual Score

Get fresh data set of FRET patients

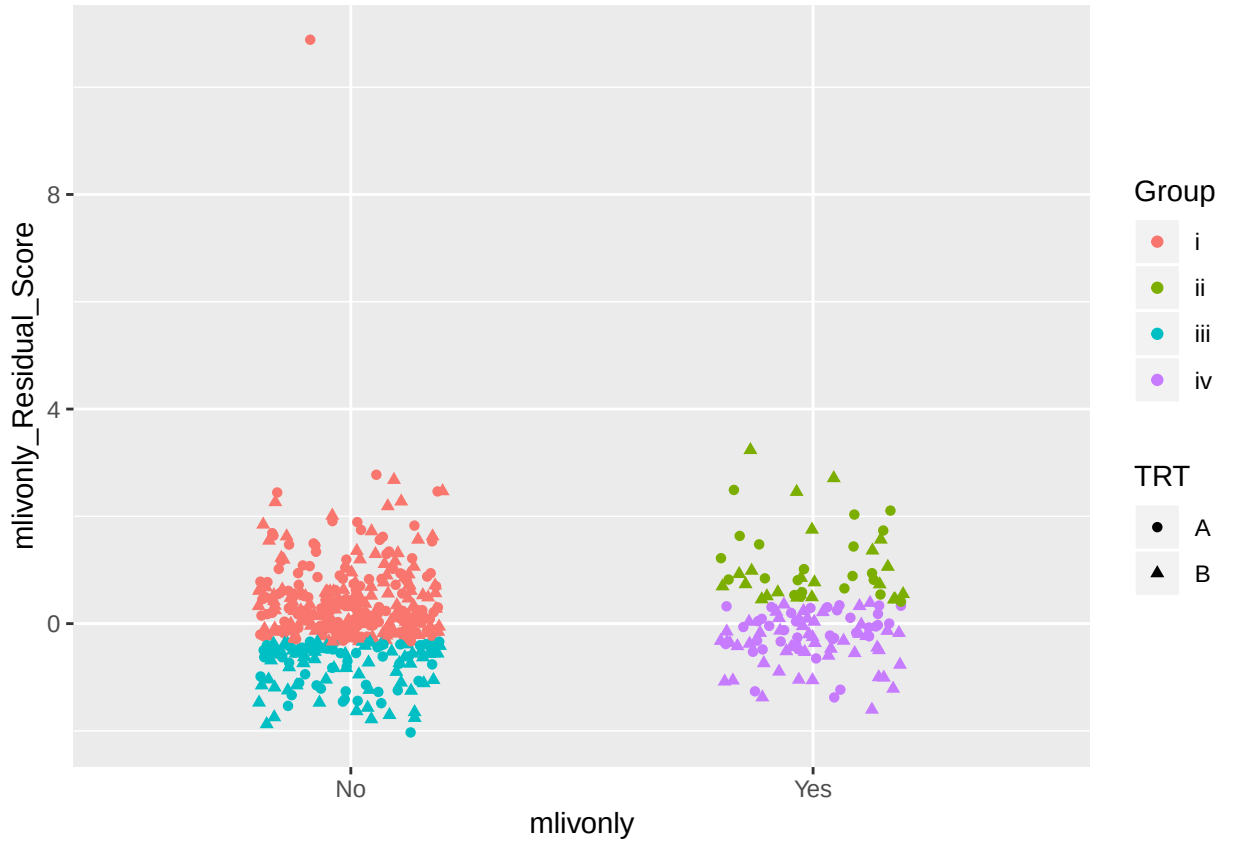
```
data <- subset(patient_data, FRET.cohort!=0)
```

Group patients according to mlivonly and predicted class

```
data$Group <- ifelse(data$mlivonly == "No",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

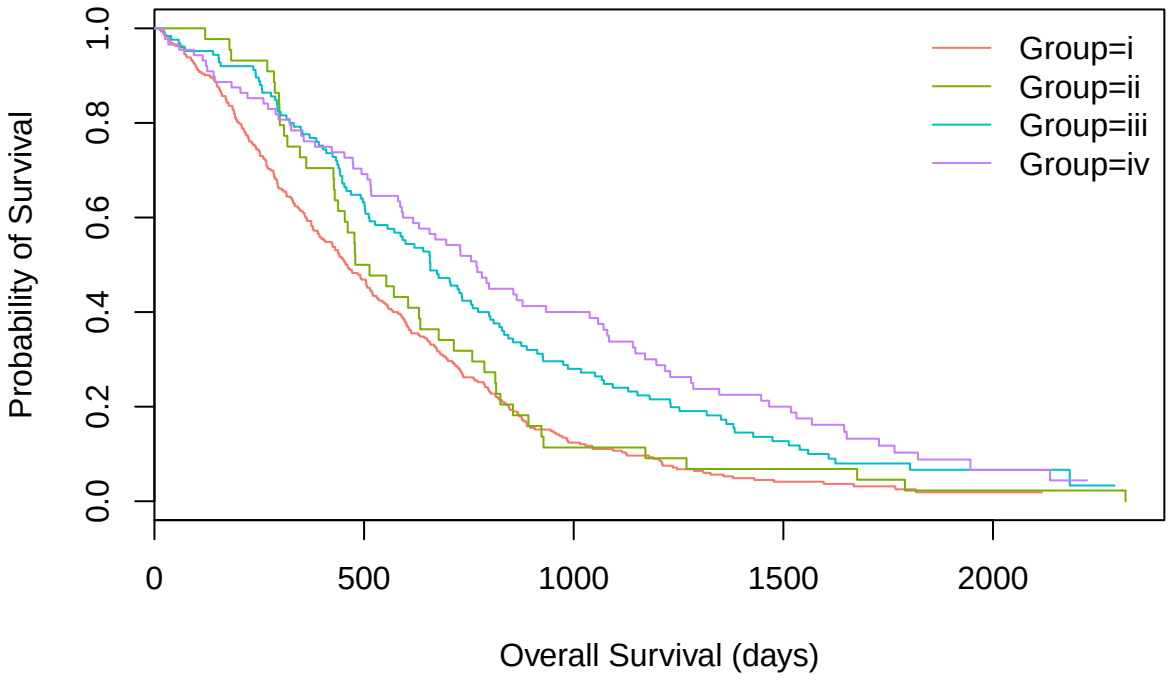
Plot mlivonly vs residual signature

```
#data <- subset(data, mlivonly_Residual_Score<8)   # one outlier: really high residual score

ggplot(data, aes(mlivonly, mlivonly_Residual_Score)) +
  geom_jitter(width=0.2, aes(color = Group, shape = TRT))
```



Plot survival curves for the groups

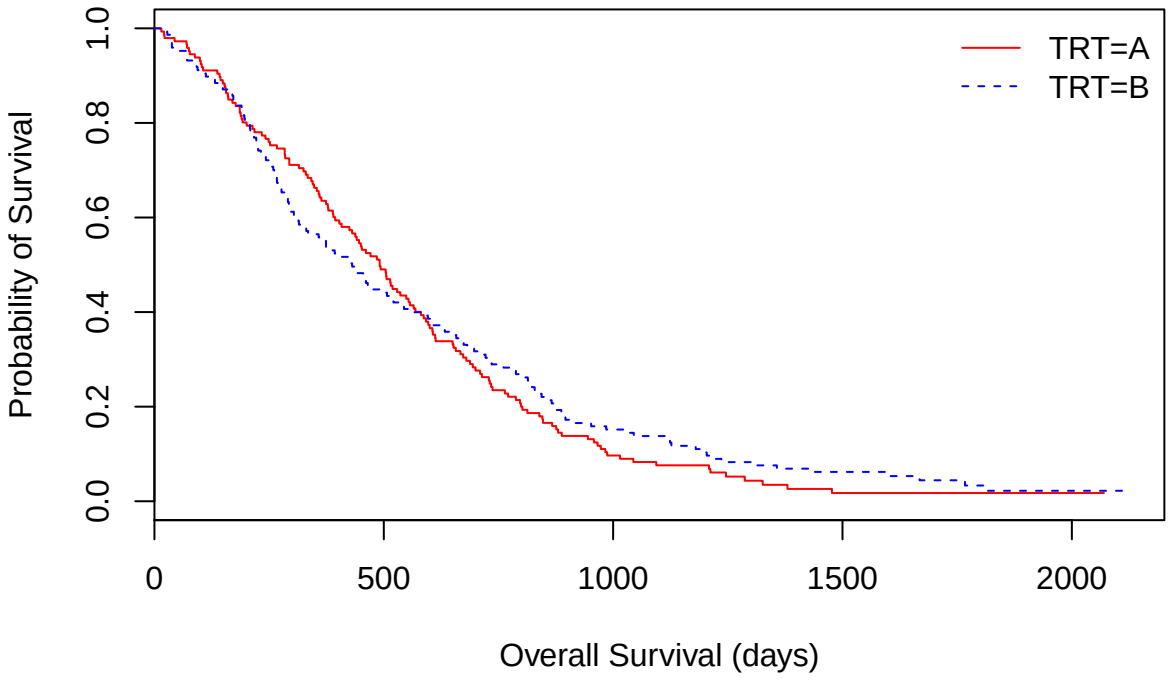
```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)

km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##              n events median 0.95LCL 0.95UCL
## Group=i    293    282    456     403     520
## Group=ii    44     44    496     438     714
## Group=iii 125    115    658     556     772
## Group=iv    88     78    768     617    1058
```

```
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



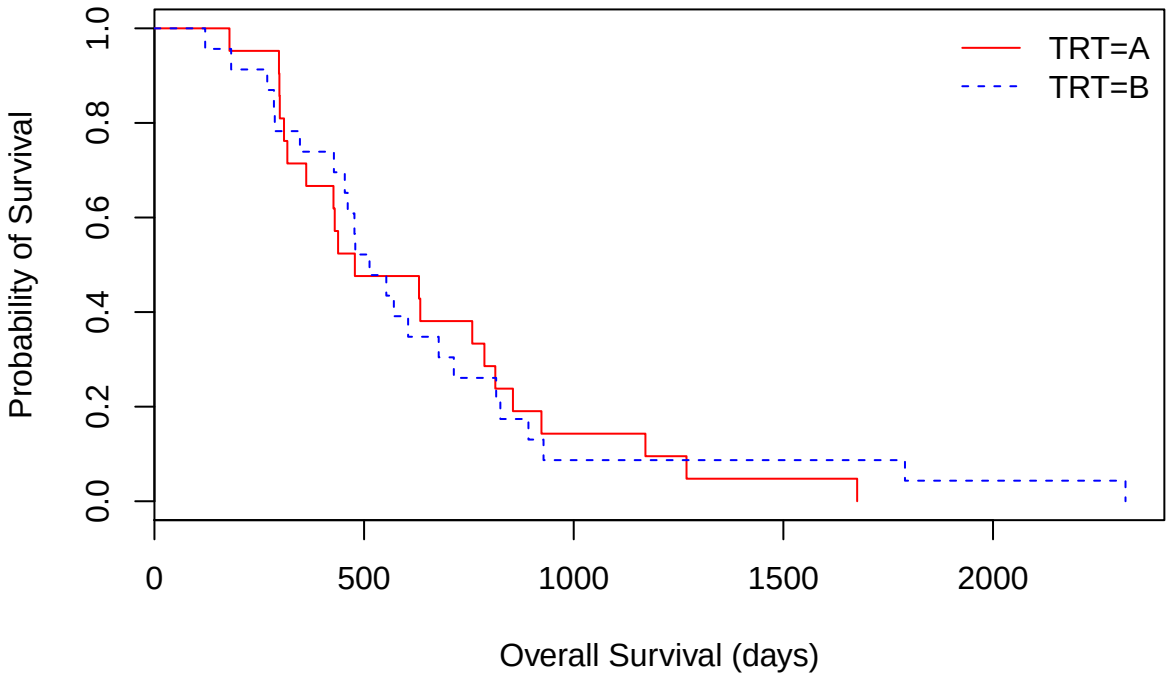

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 146    141    491     425     565
## TRT=B 147    141    431     331     544
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 146      141      136     0.212     0.415
## TRT=B 147      141      146     0.196     0.415
##
##  Chisq= 0.4  on 1 degrees of freedom, p= 0.5
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



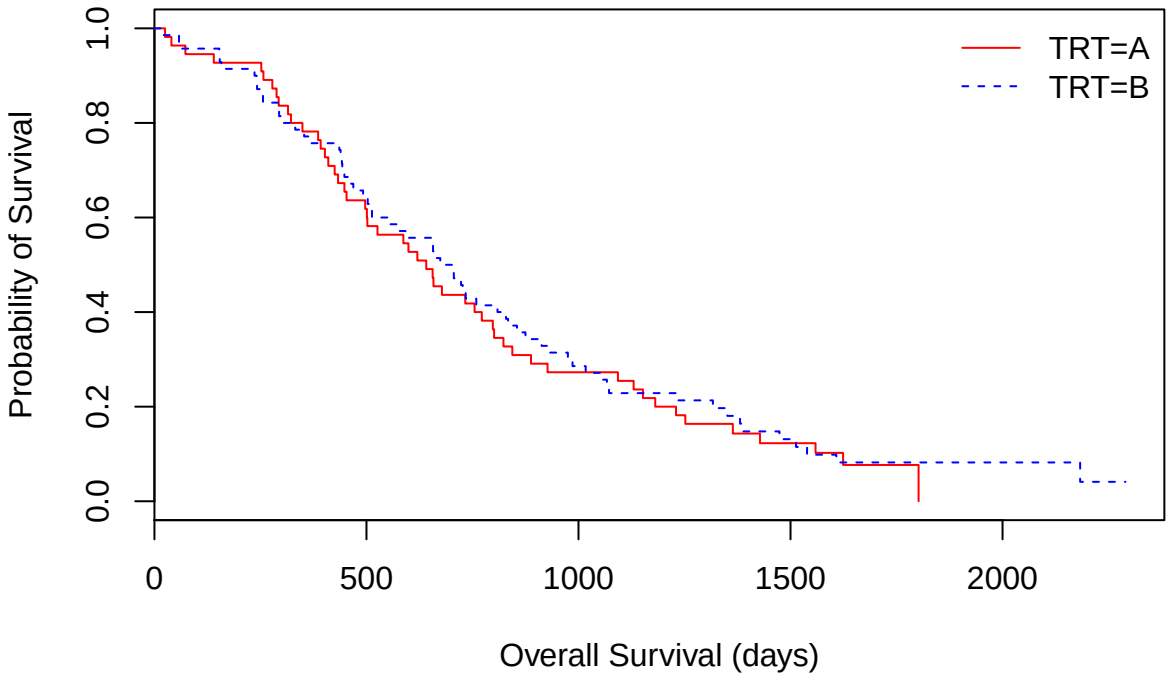

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A 21     21    478     362     855
## TRT=B 23     23    513     454     815
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 21       21     20.5    0.0128    0.0253
## TRT=B 23       23     23.5    0.0112    0.0253
##
##  Chisq= 0  on 1 degrees of freedom, p= 0.9
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



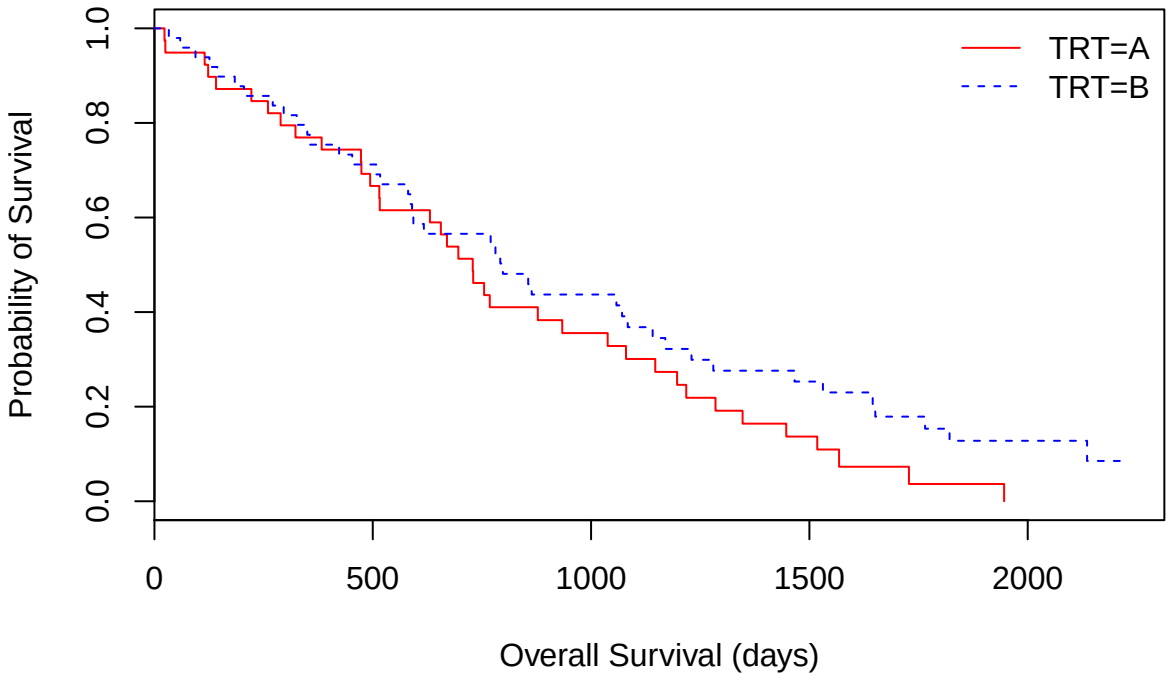

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 55     51    641     501     801
## TRT=B 70     64    689     513     855
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 55       51     48.6    0.1150     0.201
## TRT=B 70       64     66.4    0.0843     0.201
##
##  Chisq= 0.2  on 1 degrees of freedom, p= 0.7
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 39     37    729     516    1080
## TRT=B 49     41    798     590    1170
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 39       37     30.6     1.319      2.24
## TRT=B 49       41     47.4     0.853      2.24
##
##  Chisq= 2.2  on 1 degrees of freedom, p= 0.1
```

Investigate PIK3CA.Mutation vs its Residual Score

Get fresh data set of FRET patients

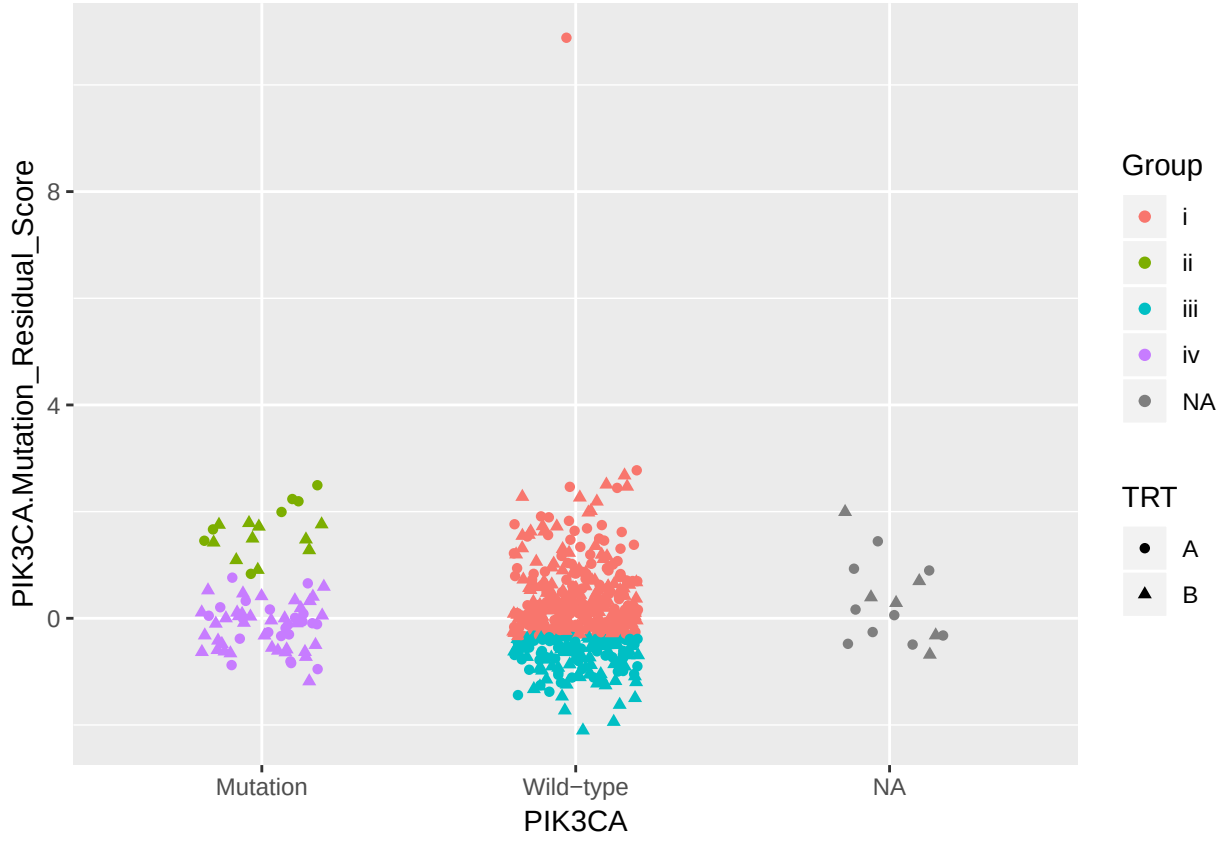
```
data <- subset(patient_data, FRET.cohort!=0)
```

Group patients according to PIK3CA.Mutation and predicted class

```
data$Group <- ifelse(data$PIK3CA == "Wild-type",
                     ifelse(data$Pred.Class == 1, "iii", "i"),
                     ifelse(data$Pred.Class == 1, "iv", "ii"))
```

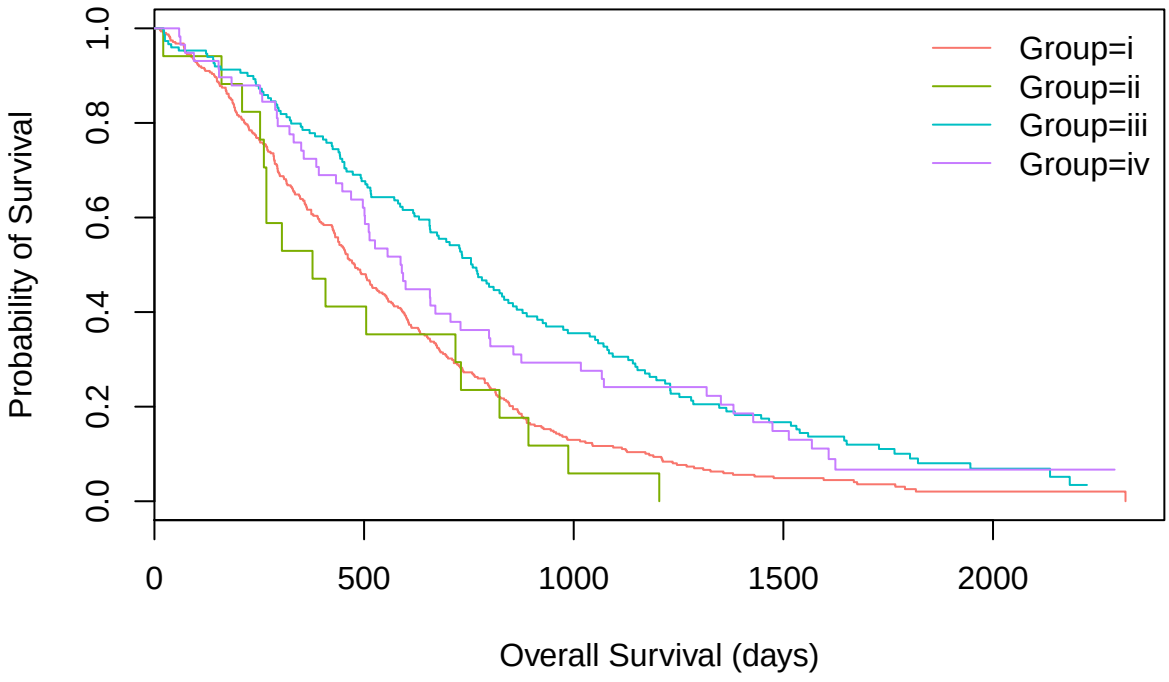
Plot PIK3CA.Mutation vs residual signature

```
#data <- subset(data, PIK3CA.Mutation_Residual_Score<8)   # one outlier: really high residual score

ggplot(data, aes(PIK3CA, PIK3CA.Mutation_Residual_Score)) +
  geom_jitter(width=0.2, aes(color = Group, shape = TRT))
```



Plot survival curves for the groups

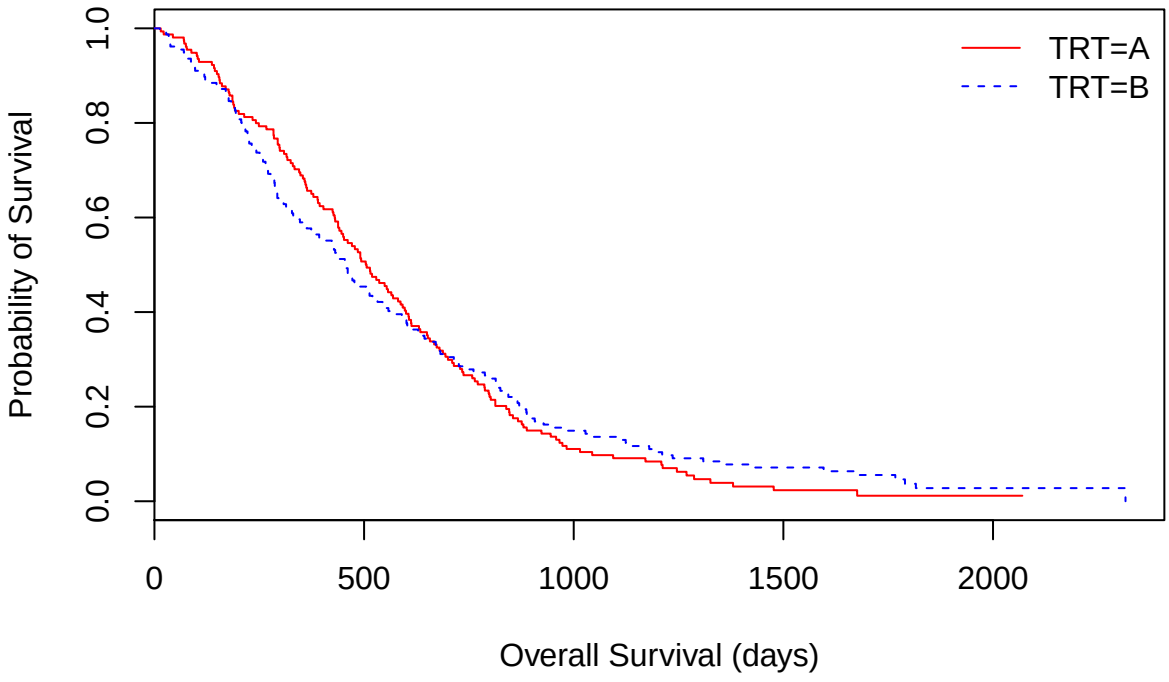
```
col=c("#F8766D", "#7CAe00", "#00BFC4", "#C77CFF") # ggplot default colours
lty=c(1)

km <- survfit(SurvObj.os ~ Group, data=data)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ Group, data = data)
##
##    15 observations deleted due to missingness
##              n events median 0.95LCL 0.95UCL
## Group=i    311    300    477     438     544
## Group=ii    17     17    377     267     823
## Group=iii 149    134    759     658     855
## Group=iv   58     53    588     501     798
```

```
col=c("red", "blue")
lty=c(1,2)

data_g <- subset(data, Group=="i")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



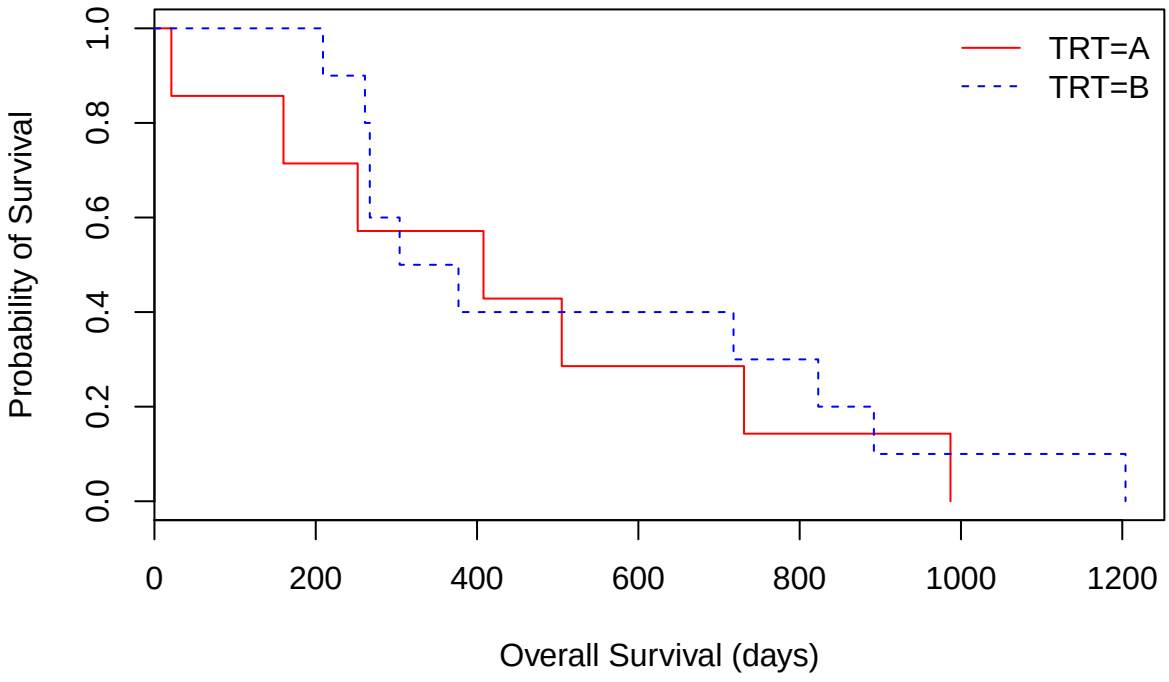

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 155    150    506     441     592
## TRT=B 156    150    455     374     553
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 155      150      147    0.0820     0.164
## TRT=B 156      150      153    0.0783     0.164
##
##  Chisq= 0.2  on 1 degrees of freedom, p= 0.7
```

```
data_g <- subset(data, Group=="ii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



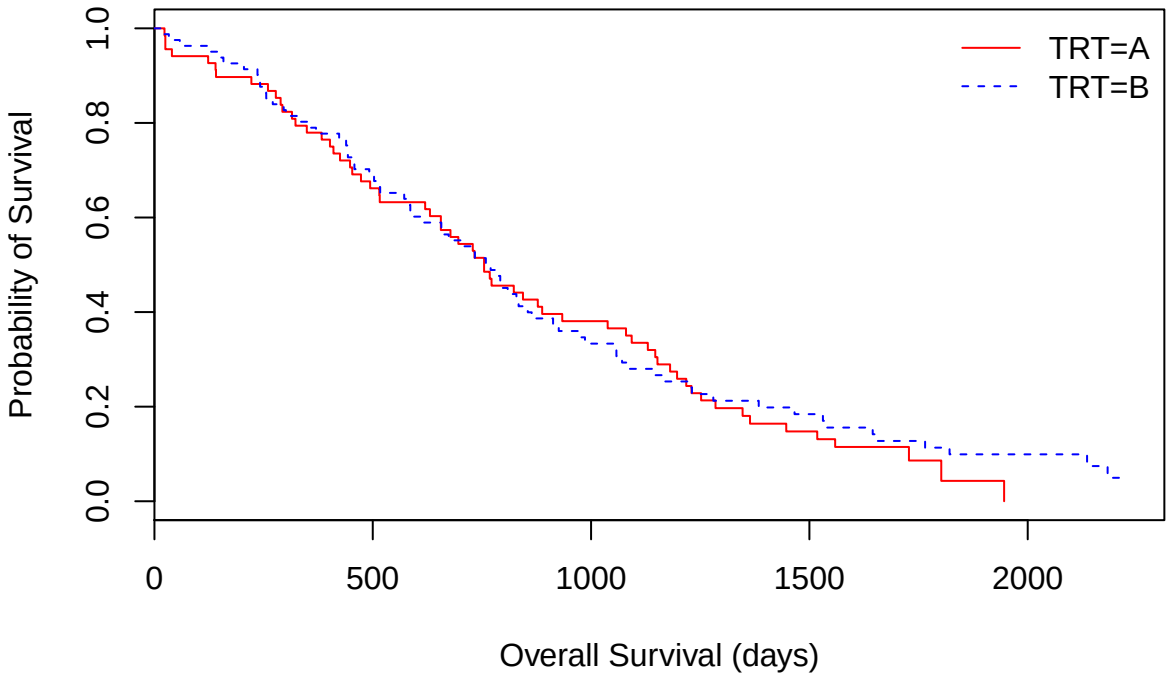

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A  7      7    408     160      NA
## TRT=B 10     10    340     267      NA
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A  7        7     6.04    0.1521     0.252
## TRT=B 10       10    10.96    0.0839     0.252
##
##  Chisq= 0.3  on 1 degrees of freedom, p= 0.6
```

```
data_g <- subset(data, Group=="iii")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```



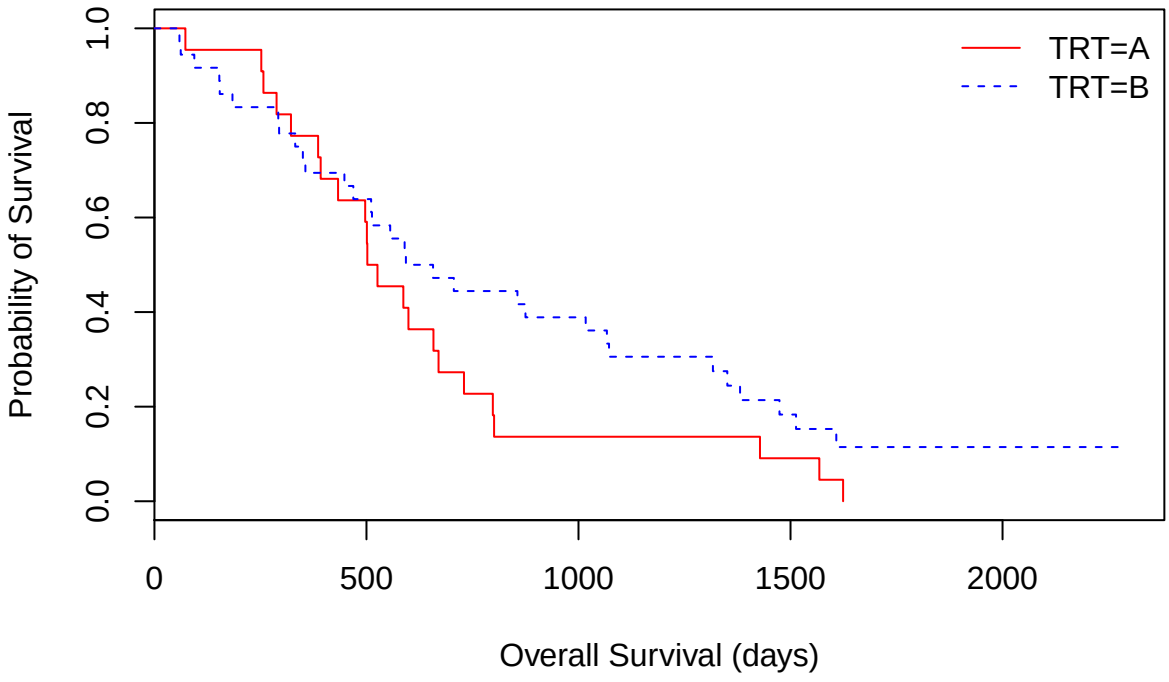

```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##         n events median 0.95LCL 0.95UCL
## TRT=A 68     62    755     631    1080
## TRT=B 81     72    770     617     913
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 68       62     59.2     0.136      0.25
## TRT=B 81       72     74.8     0.107      0.25
##
##  Chisq= 0.3  on 1 degrees of freedom, p= 0.6
```

```
data_g <- subset(data, Group=="iv")

km <- survfit(SurvObj.os ~ TRT, data=data_g)
plot(km, col=col, xlab="Overall Survival (days)", ylab="Probability of Survival", lty = lty)
legend("topright", col=col, legend = names(km$strata), lty = lty, bty="n")
```




```
print(km)
```

```
## Call: survfit(formula = SurvObj.os ~ TRT, data = data_g)
##
##        n events median 0.95LCL 0.95UCL
## TRT=A 22     22    514     433     730
## TRT=B 36     31    625     469    1072
```

```
survdiff(SurvObj.os ~ TRT, data=data_g)
```

```
## Call:
## survdiff(formula = SurvObj.os ~ TRT, data = data_g)
##
##        N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT=A 22       22     16.9     1.553      2.34
## TRT=B 36       31     36.1     0.726      2.34
##
##  Chisq= 2.3  on 1 degrees of freedom, p= 0.1
```

Other plots

```
dataA <- subset(data, TRT=="A")

ggplot(dataA, aes(FRETraw, Class_Pred_Residual_Score)) +
  geom_point(aes(color = ostime, shape = as.ordered(Pred.Class))) +
  scale_colour_gradient2()
```

```r
dataB <- subset(data, TRT=="B")

ggplot(dataB, aes(FRETraw, Class_Pred_Residual_Score)) +
  geom_point(aes(color = ostime, shape = as.ordered(Pred.Class))) +
  scale_colour_gradient2()
```

Session Information

```r
sessionInfo()
```

```
## R version 3.5.1 (2018-07-02)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 16299)
##
## Matrix products: default
##
## locale:
## [1] LC_COLLATE=English_United Kingdom.1252
## [2] LC_CTYPE=English_United Kingdom.1252
## [3] LC_MONETARY=English_United Kingdom.1252
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United Kingdom.1252
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
## [1] pROC_1.15.3        knitr_1.20         survminer_0.4.6
## [4] ggpubr_0.2         magrittr_1.5       ggplot2_3.1.1
## [7] survival_2.42-3    filesstrings_3.0.0 stringr_1.3.1
##
## loaded via a namespace (and not attached):
##  [1] zoo_1.8-4          tidyselect_0.2.5   purrr_0.2.5
##  [4] splines_3.5.1      lattice_0.20-35    colorspace_1.3-2
##  [7] generics_0.0.2     vctrs_0.2.0        htmltools_0.3.6
## [10] yaml_2.2.0         survMisc_0.5.5     rlang_0.4.0
## [13] pillar_1.4.1       glue_1.3.0         withr_2.1.2
## [16] matrixStats_0.54.0 lifecycle_0.1.0    plyr_1.8.4
## [19] munsell_0.5.0      gtable_0.2.0       evaluate_0.12
## [22] labeling_0.3       highr_0.7          broom_0.5.2
## [25] Rcpp_1.0.1         xtable_1.8-4       scales_1.0.0
## [28] backports_1.1.2    checkmate_1.9.3    km.ci_0.5-2
## [31] gridExtra_2.3      digest_0.6.18      stringi_1.2.4
## [34] dplyr_0.8.3        KMsurv_0.1-5       grid_3.5.1
## [37] rprojroot_1.3-2    tools_3.5.1        lazyeval_0.2.1
## [40] tibble_2.1.1       crayon_1.3.4       tidyr_1.0.0
## [43] pkgconfig_2.0.2    zeallot_0.1.0      Matrix_1.2-14
## [46] data.table_1.12.2  strex_1.0.1        assertthat_0.2.0
## [49] rmarkdown_1.10     R6_2.3.0           nlme_3.1-137
## [52] compiler_3.5.1
```