

gClinBiomarker: Example Use Cases

Ning Leng, Alexey Pronin, Doug Kelkhoff

2018-04-02

Contents

1	Loading packages and data	5
2	Example data set	5
3	SummaryVars(): Summarize demographics variables (check demographics imbalance)	6
3.1	Default	6
3.2	Compare to non-BEP instead of ITT	7
3.3	Allow testing	7
3.4	Reorder TRT/CTRL arm in display	8
3.5	Combine trt arms	8
3.6	Alternative BEP indicator	8
4	PlotProperty(): Plot biomarker, clinical covariate property and their association	9
4.1	Numeric biomarker variable. No clinical variables. Log transformation.	9
4.2	No biomarker variable. Two numeric clinical variables. Log transformation for one variable. . .	10
4.3	Numeric biomarker variable. Two clinical categorical variables. Log transformation for numeric variable.	10
4.4	Numeric biomarker variable. Two clinical variables: one is categorocal, second is numeric. Log transformation for biomarker (numeric) variable.	11
4.5	Categorical biomarker variable. Categorical clinical variable.	12
4.6	Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. .	13
4.7	Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Don't plot biomarker variable but plot clinical variables and association between biomarker and clinical variables.	14
4.8	Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Don't plot clinical variables but plot biomarker variable and association between biomarker and clinical variables.	15
4.9	Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Don't plot association between variables but plot biomarker and clinical variables. . . .	16
4.10	Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Plot only association between variables.	17
4.11	Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Plot only clinical variables.	18

5	PlotRspBar(): Compare response outcome across different population	19
5.1	Plot response of one population	19
5.2	Plot response of one population, binarize outcome (classify classes to responder vs non responder)	20
5.3	Change color	21
5.4	Plot horizontally	22
5.5	By arm	22
5.6	Compare full population vs BEP	24
5.7	Compare subgroups	25
5.8	Plot count instead of percentage	26
6	PlotKM(): Plot KM curves for subpopulations	27
6.1	Without subgroup	27
6.2	Without subgroup, BEP	28
6.3	By TRT	29
6.4	By TRT, change color, line type	30
6.5	Mark median PFS, no grid	31
6.6	By KRAS.mutant only	32
6.7	By TRT and KRAS.mutant	34
6.8	By TRT and KRAS.mutant, change color and line type	35
6.9	By TRT and KRAS.expression (continuous biomarker, cut at median)	36
6.10	By TRT and KRAS.expression (continuous biomarker, cut at a numerical cutoff)	37
6.11	By TRT and KRAS.expression (continuous biomarker, cut at a numerical cutoff). High group defined as “greater than”, instead of “greater than or equal to”	38
6.12	By TRT and KRAS.expression , more than 2 groups	39
6.13	More flexibility, reorder subgroups	41
6.14	By TRT and KRAS.mutant, reorder and rename	42
6.15	Legend location	43
7	PlotTabForestBiomarker() : forest plot and summary statistics table for a single biomarker (include cutoff exploration for cont. biomarker)	44
7.1	Survival outcome, 2-arm, categorical variable	44
7.2	Survival outcome, another format	46
7.3	Survival outcome, 2-arm, categorical variable, don’t show ITT, BEP, rename variable name in display	47
7.4	Survival outcome, 2-arm, continuous variable, greater than some percentage cutoffs	49
7.5	Survival outcome, 2-arm, continuous variable, less than some percentage cutoffs	50
7.6	Survival outcome, 2-arm, continuous variable, greater and less than some percentage cutoffs	52
7.7	Survival outcome, 2-arm, continuous variable, within cutoff bin	55

7.8	Survival outcome, 2-arm, continuous variable, greater than some numerical cutoffs	56
7.9	Survival outcome, 2-arm, continuous variable, adjust for covariates	57
7.10	Survival outcome, 2-arm, continuous variable, stratification	59
7.11	Survival outcome, 2-arm, continuous variable, adjust for covariates and stratified by strata . .	60
7.12	Survival outcome, 1arm	61
7.13	Survival outcome, 2arm, flip TRT/CTRL order (calculate ctrl over trt HR)	63
7.14	Survival outcome, 2-arm, continuous variable, greater than some percentage cutoffs, show across-arm and within-arm results in the same plot	64
7.15	Response outcome, 2-arm, categorical variable	66
7.16	Response outcome, another format	68
7.17	Continuous outcome, 2-arm, categorical variable	69
8	PlotTabForestMulti(): Forest plots to compare multiple variates' effect in ITT vs BEP, or compare multiple variates' effect in subpopulations	72
8.1	2-arm, compare BEP vs ITT	72
8.2	2-arm, compare subgroups defined by biomarker	74
8.3	2-arm, compare subgroups defined by biomarker, also show ITT	74
8.4	2-arm, compare subgroups defined by biomarker, also show BEP	75
8.5	1-arm, compare ITT vs BEP	79
8.6	2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker .	79
8.7	2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker, calculate "< cutoff"	81
8.8	2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker, calculate within bin statistics	83
8.9	Basic forest plot without comparison	84
8.10	Response outcome	84
8.11	Continuous endpoint	86
9	PlotSTEPP(): STEPP (Subpopulation Treatment Effect Pattern Plot) from the given point estimates and confidence intervals at desired percentiles.	88
9.1	Survival outcome	88
9.2	Continuous outcome	90
9.3	Binary outcome variable	91
10	CoxTab(): fit cox proportional model for multiple covariates (additive model or separate models)	93
10.1	single covariate	93
10.2	multiple covariates, ITT	93
10.3	BEP	94
10.4	Reorder Sex: M as reference	94
10.5	Fit separate models for each variable instead of fitting an additive model	94

11 SummaryTwoGroups()	95
11.1 Contunuous outcome	95
11.2 Binary outcome	96
11.3 Survival variable	96
12 LogRankTab(): log rank test for subgroup analysis	97
13 BoxPlot(): advanced box plot function	97
13.1 Generate example dataset	97
13.2 Specify data as named list	98
13.3 Same plot, now horizontally plotted	98
13.4 Specify data as numeric matrix	99
13.5 Specify data as numeric (unnamed) vectors	99
13.6 ... horizontally plotted (no axis-label rotation done here)	100
13.7 Plot values 'y' according to time 'time' (factor levels are automatically ordered as e.g. function sort does)	100
13.8 Now as box-percentile plot	101
13.9 With custom main title	101
13.10The same plot with trend line (connects either means or medians) and Y-axis label	102
13.11Use an addition grouping variable to color points in the stripchart	103
13.12Use yet another grouping factor for plotting symbols in the stripchart	103
13.13Generate new dataset with different stucture	104
13.14Boxplot with trend lines (mean) and grid added to the plot	104
13.15Now as box-percentile plot	105
13.16Use yet another way to specify the data	105
13.17Specifying data as numeric matrix and using a trend-line connecting the means	106
13.18Multiple grouping factors can be specified via the formula interface which is exemplified using the mtcars dataset, of interest is miles per gallon (mpg) depending on number of gears and on the number of cylinders	106
13.19Now 'cyl' is explicitly nested within 'gear' which changes the ordering of combined grouping factors (which is identical to using formula 'mpg~cyl:gear').	107
13.20More meaningful group-labels are best specified using custom factor-level names (increase width of the plot window)	107
13.21One can use a table as Xaxis label representing the factor-level combination defining sub-classes	108
13.22With the original factor levels and as horizontal plot	108
13.23Using smaller bottom margin will result in smaller table height	109
13.24One can use different font-settings for rownames and cells of the table	110
13.25Use more crossed factors	110

13.26	Alternatively one can use the ‘Xaxis’ argument, but the ordering of these labels is not checked which is not important for automatically generated group-labels as shown in the previous example	111
13.27	The same plot with some fancy options	112
13.28	Horizontal fancy plot	112
14	Longitudinal analysis	113
14.1	Biomarker Endpoint Progression	113
14.2	Plotting Subpopulations	115
14.3	Including sample counts	116
14.4	Plotting Deviations as Errorbars	117

1 Loading packages and data

```
if (!require(gClinBiomarker)) {
  install_github("RPackages/gClinBiomarker", host="https://github.roche.com/api/v3")
  library(gClinBiomarker)
}

library(knitr)
library(devtools)
library(ggplot2)
data(input)
sample.data <- input
```

2 Example data set

```
head(sample.data)
```

```
## Patient.ID Sample.ID Arm Age Weight ECOG Sex Baseline.SLD Country
## 1 PID001 SID001 TRT 40 61.0 0 F 550.4970 Western Europe
## 2 PID002 SID002 TRT 60 87.0 1 F 549.7751 USA
## 3 PID003 SID003 TRT 53 57.6 1 M 548.8829 Western Europe
## 4 PID004 SID004 TRT 44 57.0 0 F 549.6050 USA
## 5 PID005 SID005 TRT 49 72.5 2 F 551.5498 Other
## 6 PID006 SID006 TRT 62 76.0 0 M 549.2565 Other
## CD8.ihc KRAS.mutant KRAS.exprs OS PFS Response BEP OS.event
## 1 3 Mutant 171.25 9.691992 5.782341 PR 1 0
## 2 2 Wild Type 2.77 4.435318 1.412731 PD 1 1
## 3 3 Wild Type 61.82 9.691992 1.215606 PD 1 0
## 4 1 Mutant 71.51 1.905544 1.905544 PD 1 0
## 5 NA <NA> NA 2.628337 2.628337 SD 0 1
## 6 2 Mutant 44.63 4.829569 4.139630 NON CR/PD 1 0
## PFS.event Lab_ontrt
## 1 0 28.993922
```

```
## 2      1  9.890427
## 3      1 26.896020
## 4      1  5.421392
## 5      1 14.741382
## 6      0 16.957035
```

```
str(sample.data)
```

```
## 'data.frame':   550 obs. of  19 variables:
## $ Patient.ID : chr  "PID001" "PID002" "PID003" "PID004" ...
## $ Sample.ID : chr  "SID001" "SID002" "SID003" "SID004" ...
## $ Arm : Factor w/ 2 levels "CTRL","TRT": 2 2 2 2 2 2 2 2 2 1 ...
## $ Age : int  40 60 53 44 49 62 70 49 62 45 ...
## $ Weight : num  61 87 57.6 57 72.5 76 46 69.3 65 54 ...
## $ ECOG : int  0 1 1 0 2 0 0 1 0 1 ...
## $ Sex : chr  "F" "F" "M" "F" ...
## $ Baseline.SLD: num  550 550 549 550 552 ...
## $ Country : Factor w/ 3 levels "Other","USA",...: 3 2 3 2 1 1 3 3 3 1 ...
## $ CD8.ihc : num  3 2 3 1 NA 2 NA 1 NA NA ...
## $ KRAS.mutant : Factor w/ 2 levels "Mutant","Wild Type": 1 2 2 1 NA 1 NA 2 NA NA ...
## $ KRAS.exprs : num  171.25 2.77 61.82 71.51 NA ...
## $ OS : num  9.69 4.44 9.69 1.91 2.63 ...
## $ PFS : num  5.78 1.41 1.22 1.91 2.63 ...
## $ Response : Factor w/ 6 levels "CR","NE","NON CR/PD",...: 5 4 4 4 6 3 4 3 4 6 ...
## $ BEP : num  1 1 1 1 0 1 0 1 0 0 ...
## $ OS.event : int  0 1 0 0 1 0 0 0 1 0 ...
## $ PFS.event : int  0 1 1 1 1 0 1 0 1 0 ...
## $ Lab_ontrt : num  28.99 9.89 26.9 5.42 14.74 ...
```

3 SummaryVars(): Summarize demographics variables (check demographics imbalance)

3.1 Default

```
kable(
  SummaryVars(data=sample.data,trt='Arm', subgroup='BEP', var=c('Age','Sex'),
    var.class=c("numeric","categorical"))
)
```

	All(CTRL)	BEP(CTRL)	All(TRT)	BEP(TRT)
Age				
N	182	81	368	176
Mean	52.54	53.1	54.03	54.42
Median	51.5	52	54	54
Min-Max	27...85	32...85	30...89	33...89
NA's	0	0	0	0
Sex				
Total (non-NA)	182	81	368	176
NA's	0	0	0	0

	All(CTRL)	BEP(CTRL)	All(TRT)	BEP(TRT)
F	89 (48.9%)	39 (48.15%)	184 (50%)	90 (51.14%)
M	93 (51.1%)	42 (51.85%)	184 (50%)	86 (48.86%)

3.2 Compare to non-BEP instead of ITT

```
kable(
  SummaryVars(data=sample.data, trt='Arm', subgroup='BEP', var=c('Age', 'Sex'),
    var.class=c("numeric", "categorical"), compare.subgroup=TRUE)
)
```

	BEP_1(CTRL)	BEP_0(CTRL)	BEP_1(TRT)	BEP_0(TRT)
Age				
N	81	101	176	192
Mean	53.1	52.09	54.42	53.67
Median	52	50	54	54
Min-Max	32...85	27...82	33...89	30...79
NA's	0	0	0	0
Sex				
Total (non-NA)	81	101	176	192
NA's	0	0	0	0
F	39 (48.15%)	50 (49.5%)	90 (51.14%)	94 (48.96%)
M	42 (51.85%)	51 (50.5%)	86 (48.86%)	98 (51.04%)

3.3 Allow testing

```
kable(
  SummaryVars(data=sample.data, trt='Arm', subgroup='BEP', var=c('Age', 'Sex'),
    var.class=c("numeric", "categorical"), test.subgroup=TRUE)
)
```

test.subgroup is TRUE but compare.subgroup is FALSE. Set compare.subgroup to TRUE

	BEP_1(CTRL)	BEP_0(CTRL)	pvalue(CTRL)	BEP_1(TRT)	BEP_0(TRT)	pvalue(TRT)
Age						
N	81	101	0.5	176	192	0.69
Mean	53.1	52.09		54.42	53.67	
Median	52	50		54	54	
Min-Max	32...85	27...82		33...89	30...79	
NA's	0	0		0	0	
Sex						
Total (non-NA)	81	101	0.88	176	192	0.75
NA's	0	0		0	0	
F	39 (48.15%)	50 (49.5%)		90 (51.14%)	94 (48.96%)	
M	42 (51.85%)	51 (50.5%)		86 (48.86%)	98 (51.04%)	

3.4 Reorder TRT/CTRL arm in display

```
kable(
  SummaryVars(data=sample.data, trt='Arm', subgroup='BEP', var=c('Age', 'Sex'),
    var.class=c("numeric", "categorical"), trt.order=c("TRT", "CTRL"))
)
```

	All(TRT)	BEP(TRT)	All(CTRL)	BEP(CTRL)
Age				
N	368	176	182	81
Mean	54.03	54.42	52.54	53.1
Median	54	54	51.5	52
Min-Max	30...89	33...89	27...85	32...85
NA's	0	0	0	0
Sex				
Total (non-NA)	368	176	182	81
NA's	0	0	0	0
F	184 (50%)	90 (51.14%)	89 (48.9%)	39 (48.15%)
M	184 (50%)	86 (48.86%)	93 (51.1%)	42 (51.85%)

3.5 Combine trt arms

```
kable(
  SummaryVars(data=sample.data, subgroup='BEP', var=c('Age', 'Sex'),
    var.class=c("numeric", "categorical"))
)
```

	All	BEP
Age		
N	550	257
Mean	53.53	54
Median	53	54
Min-Max	27...89	32...89
NA's	0	0
Sex		
Total (non-NA)	550	257
NA's	0	0
F	273 (49.64%)	129 (50.19%)
M	277 (50.36%)	128 (49.81%)

3.6 Alternative BEP indicator

```
sample.data$BEP2 <- ifelse(sample.data$BEP==1, "Yes", "No")
kable(
  SummaryVars(data=sample.data, trt='Arm', subgroup='BEP2', var=c('Age', 'Sex'),
```



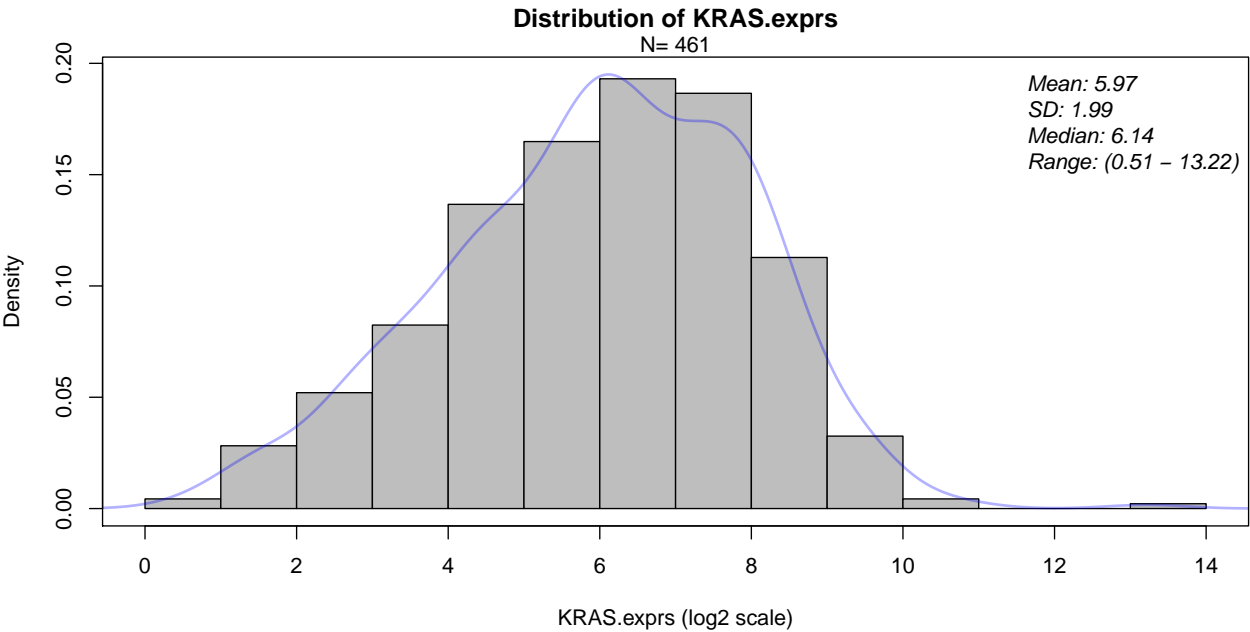
```
var.class=c("numeric","categorical"), subgroup.indicator="Yes")
)
```

	All(CTRL)	BEP2(CTRL)	All(TRT)	BEP2(TRT)
Age				
N	182	81	368	176
Mean	52.54	53.1	54.03	54.42
Median	51.5	52	54	54
Min-Max	27...85	32...85	30...89	33...89
NA's	0	0	0	0
Sex				
Total (non-NA)	182	81	368	176
NA's	0	0	0	0
F	89 (48.9%)	39 (48.15%)	184 (50%)	90 (51.14%)
M	93 (51.1%)	42 (51.85%)	184 (50%)	86 (48.86%)

4 PlotProperty(): Plot biomarker, clinical covariate property and their association

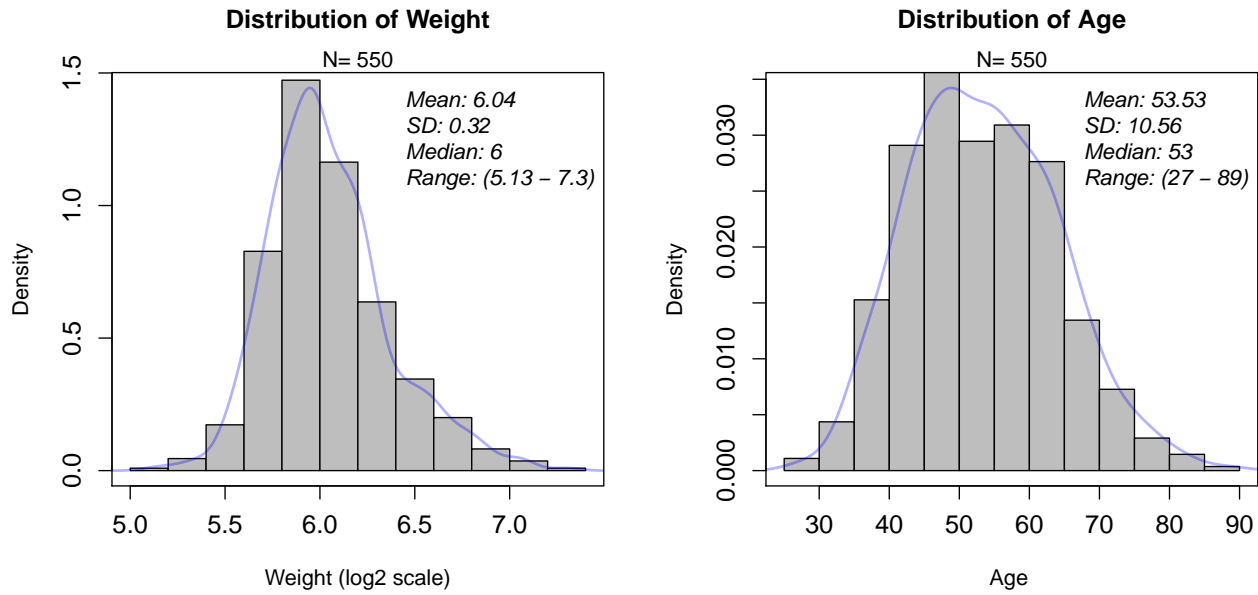
4.1 Numeric biomarker variable. No clinical variables. Log transformation.

```
PlotProperty(data=input, biomarker.var="KRAS.exprs", biomarker.class="numeric", log2=TRUE)
```



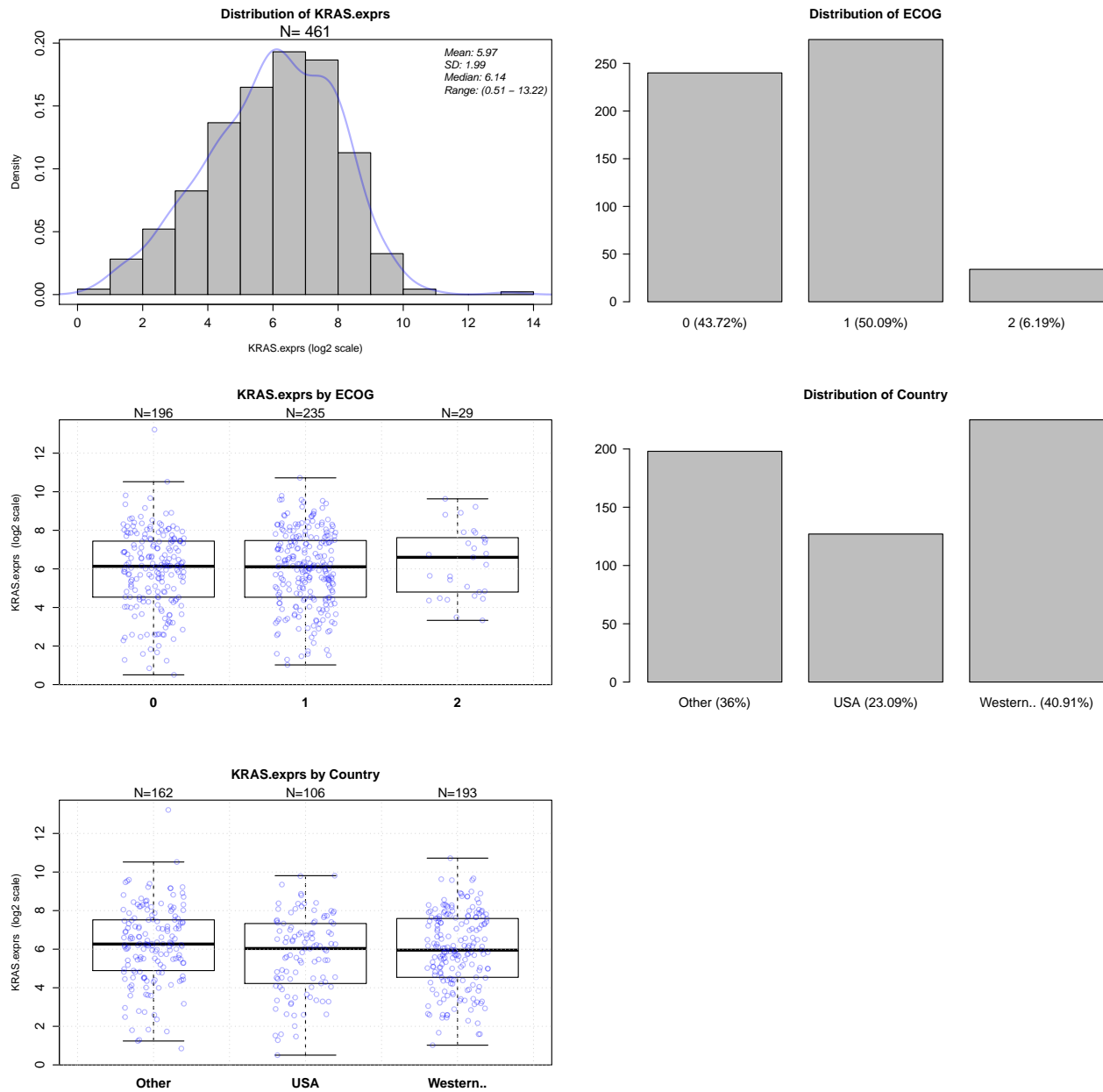
4.2 No biomarker variable. Two numeric clinical variables. Log transformation for one variable.

```
PlotProperty(data=input, biomarker.var=NULL, biomarker.class=NULL,  
var=c("Weight", "Age"), var.class=c("numeric", "numeric"),  
log2=c(TRUE, FALSE), par.param = list(mfrow=c(1,2), cex.axis=1.2))
```



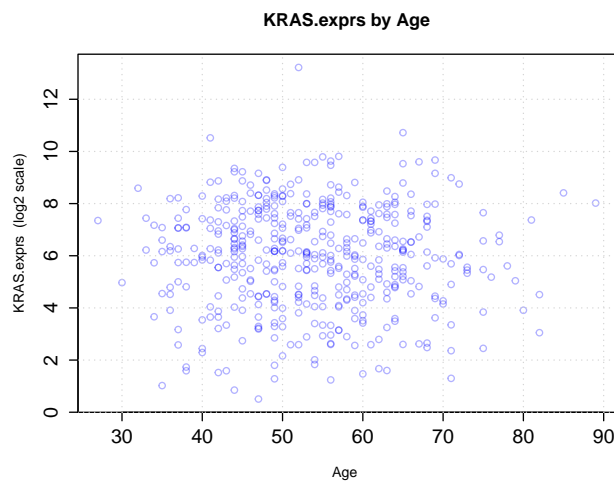
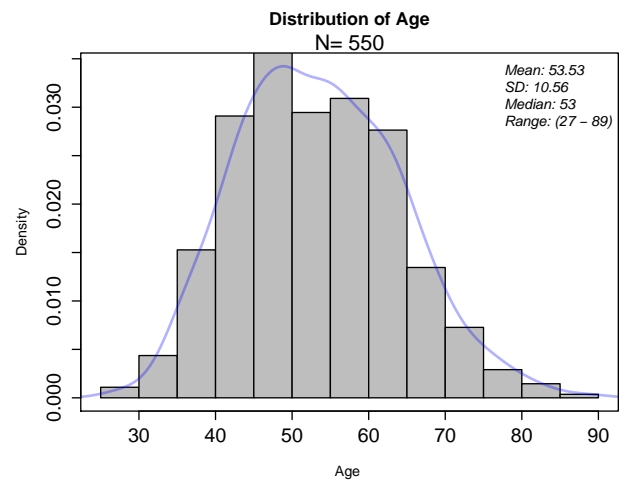
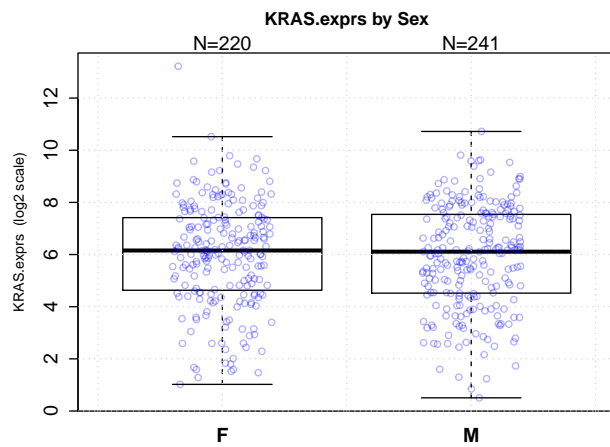
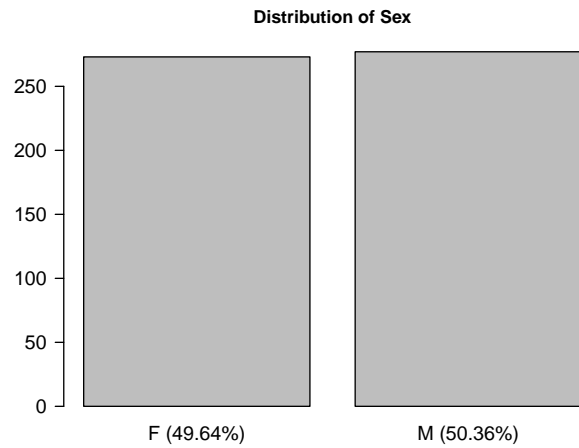
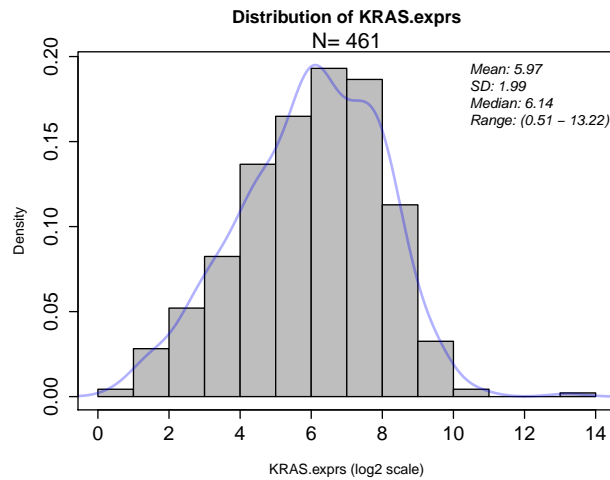
4.3 Numeric biomarker variable. Two clinical categorical variables. Log transformation for numeric variable.

```
PlotProperty(data=input, biomarker.var="KRAS.exprs", biomarker.class="numeric",  
var=c("ECOG", "Country"), var.class=c("categorical", "categorical"),  
log2=TRUE, par.param = list(mfrow=c(3,2), cex.axis=1.2),  
show.clinical.uni=TRUE)
```



4.4 Numeric biomarker variable. Two clinical variables: one is categorical, second is numeric. Log transformation for biomarker (numeric) variable.

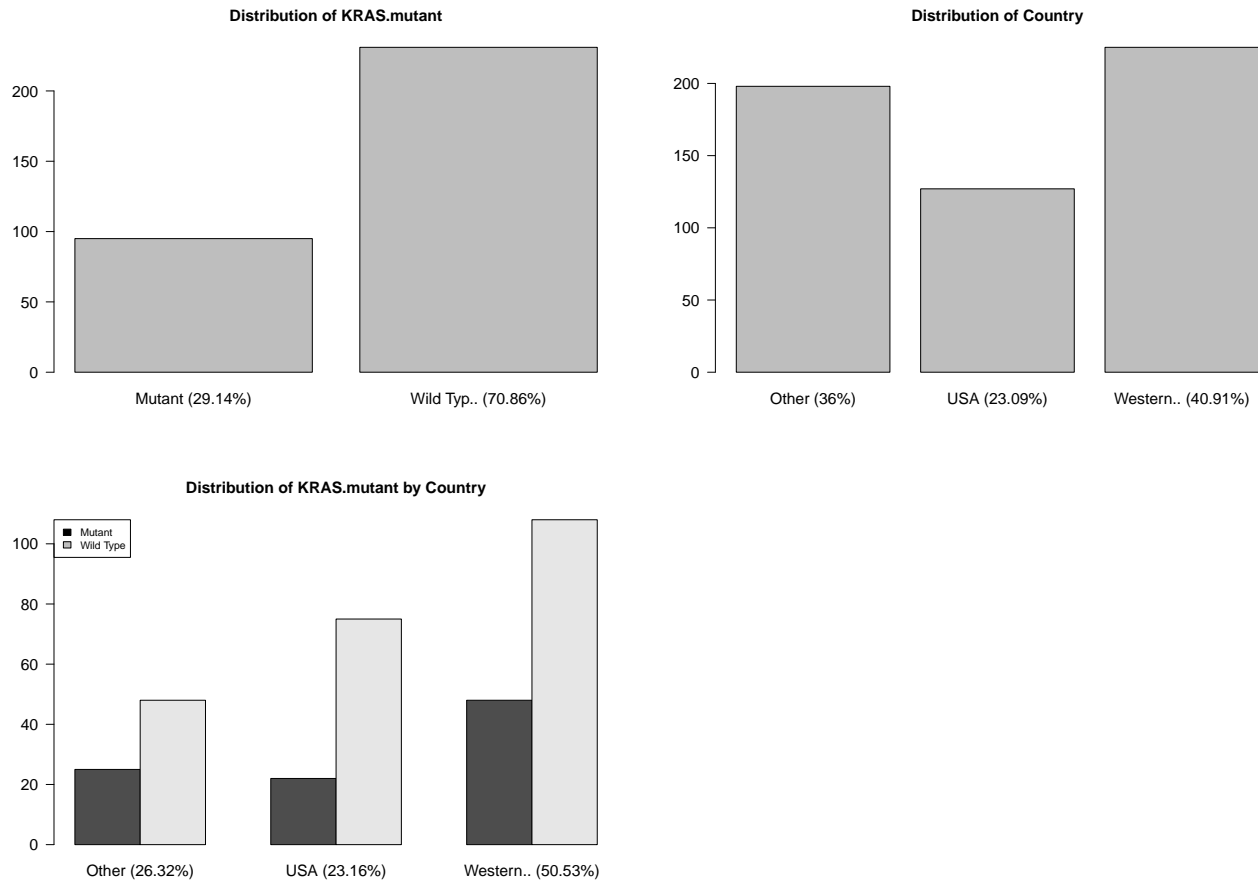
```
PlotProperty(data=input, biomarker.var="KRAS.exprs", biomarker.class="numeric",
var=c("Sex", "Age"), var.class=c("categorical", "numeric"),
log2=c(TRUE, FALSE, FALSE), par.param = list(mfrow=c(3,2), cex.axis=1.4),
show.clinical.uni=TRUE)
```



4.5 Categorical biomarker variable. Categorical clinical variable.

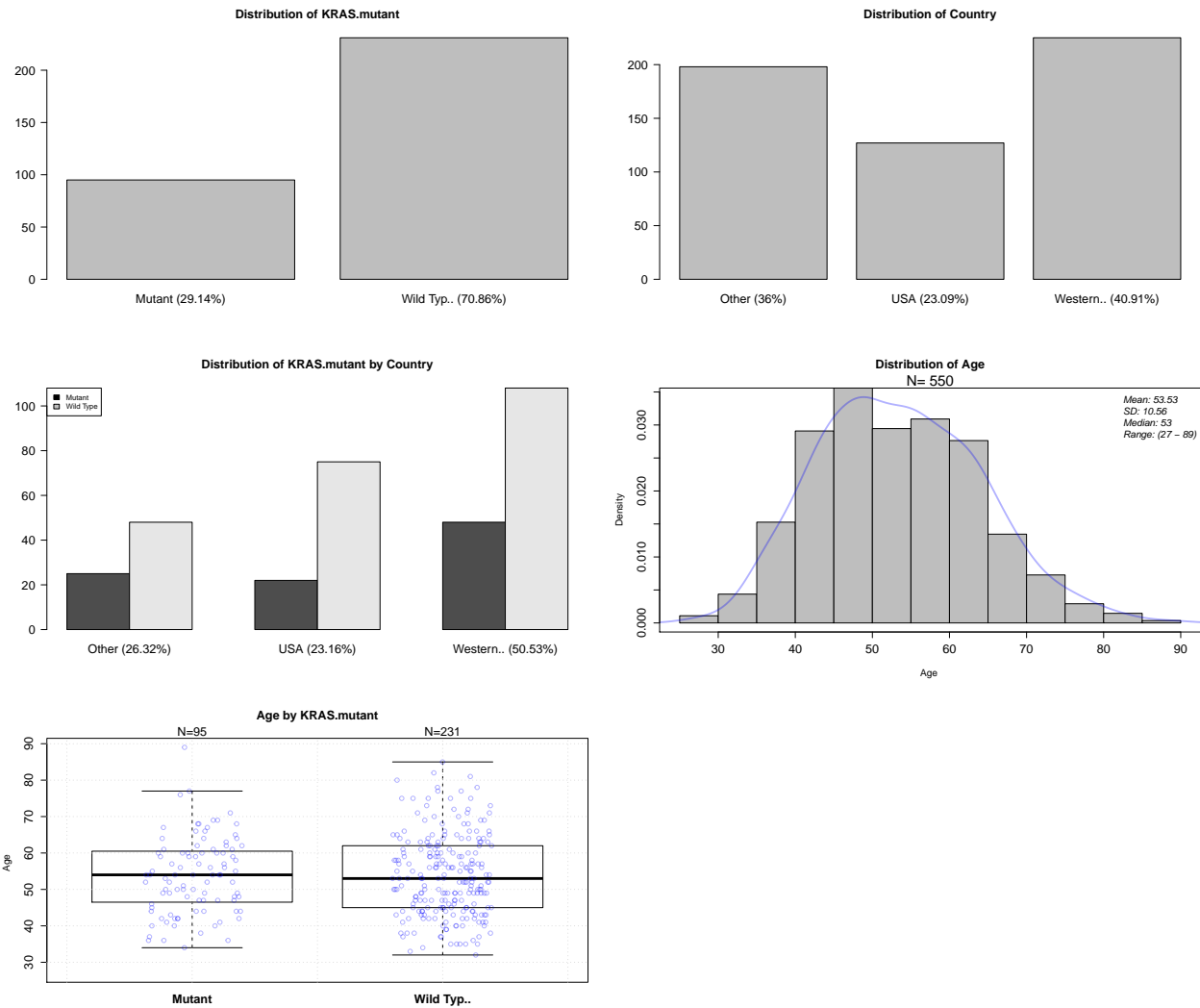
```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
             var="Country", var.class="categorical",
```

```
par.param = list(mfrow=c(2,2), cex.axis=1.2),
show.clinical.uni=TRUE)
```



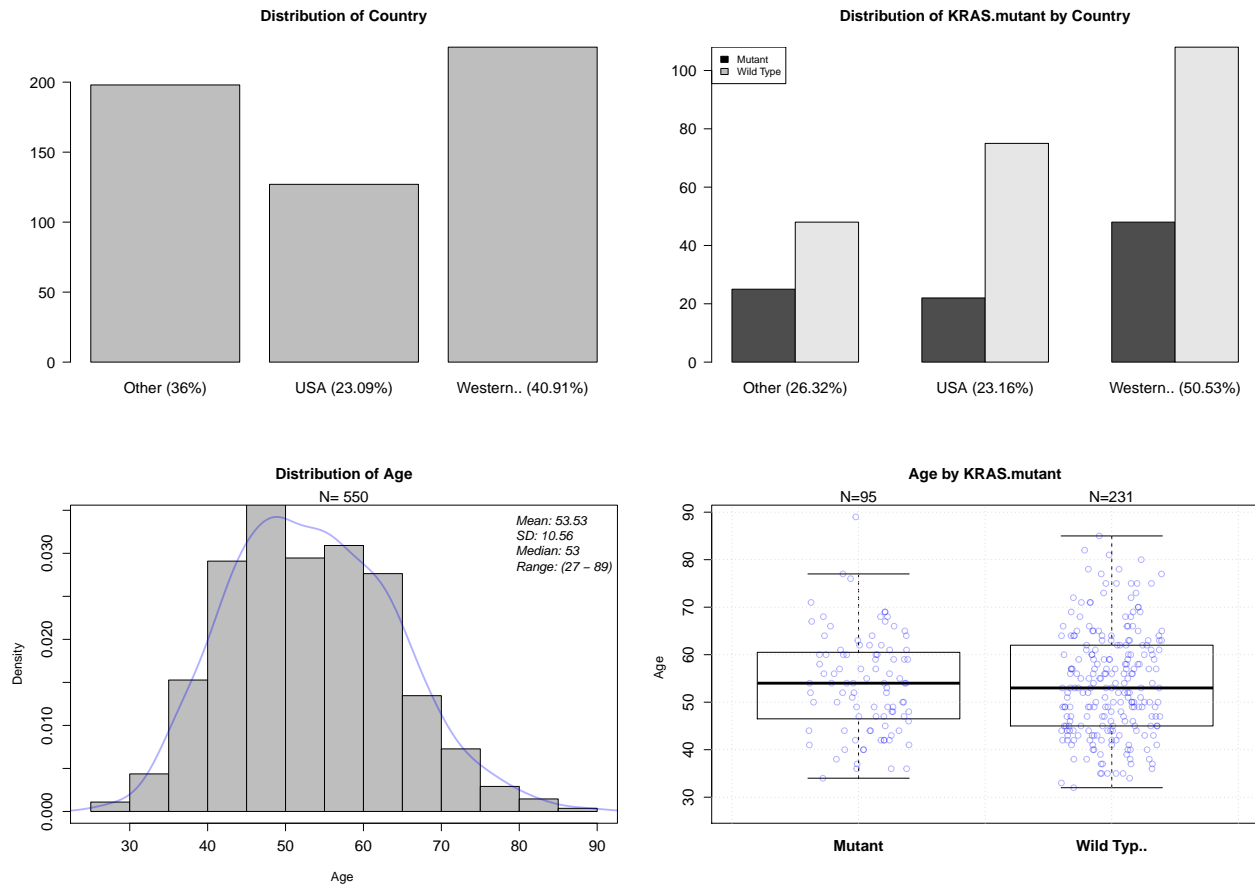
4.6 Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(mfrow=c(3,2), cex.axis=1.2),
show.clinical.uni=TRUE)
```



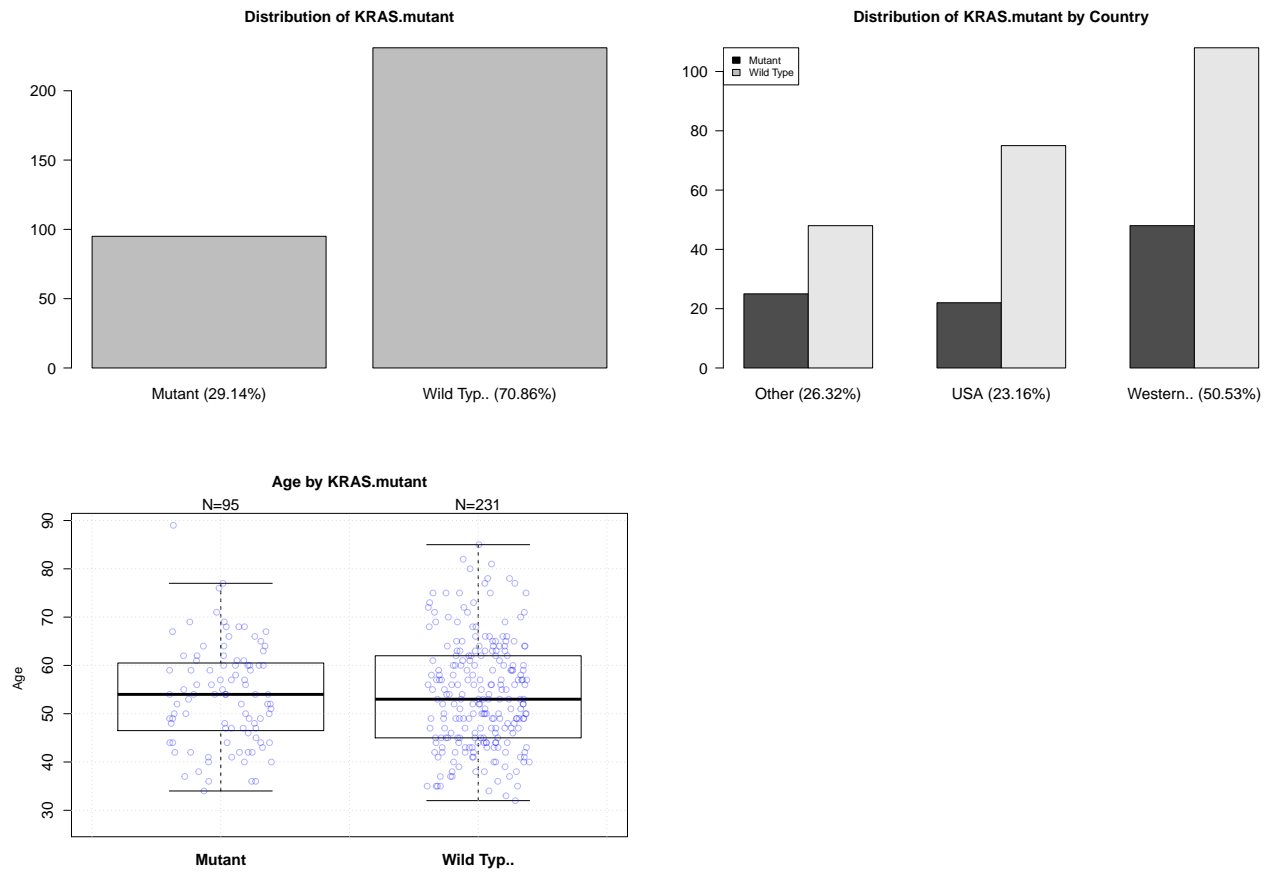
4.7 Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Don't plot biomarker variable but plot clinical variables and association between biomarker and clinical variables.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(mfrow=c(2,2), cex.axis=1.2), show.biomarker.uni = FALSE,
show.clinical.uni=TRUE)
```



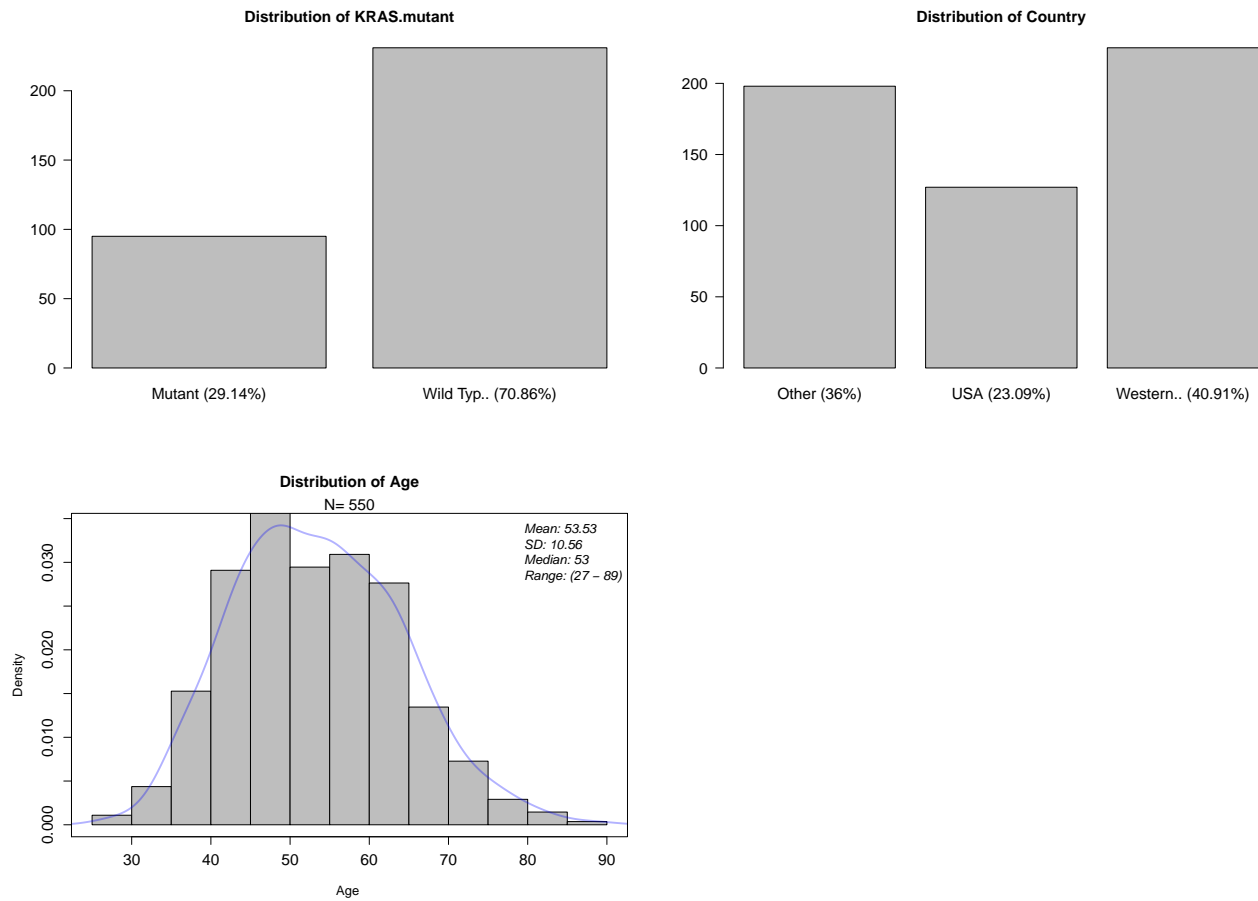
4.8 Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Don't plot clinical variables but plot biomarker variable and association between biomarker and clinical variables.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(mfrow=c(2,2), cex.axis=1.2))
```



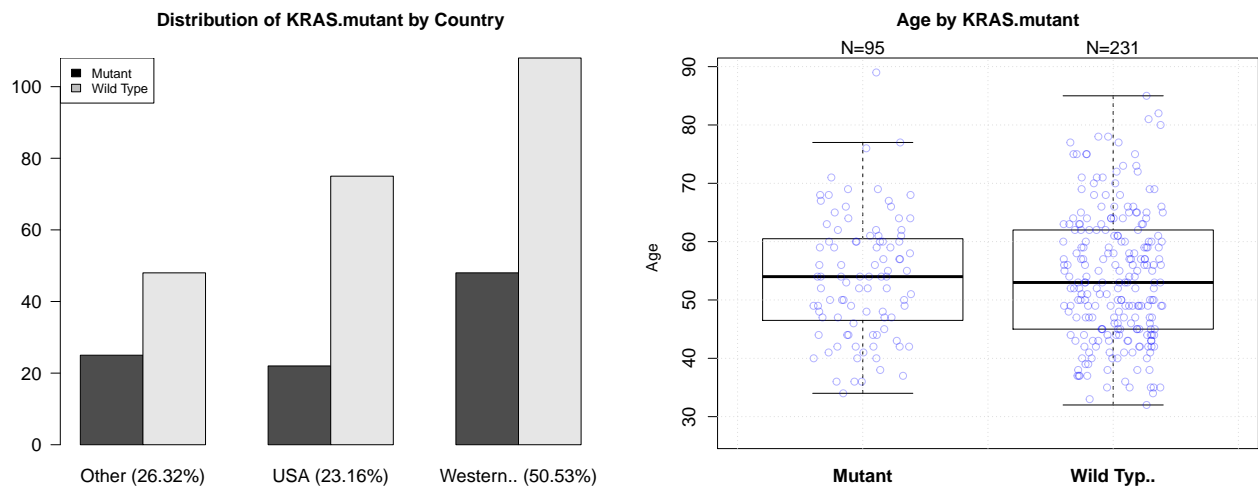
4.9 Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Don't plot association between variables but plot biomarker and clinical variables.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(mfrow=c(2,2), cex.axis=1.2), show.association = FALSE,
show.clinical.uni=TRUE)
```

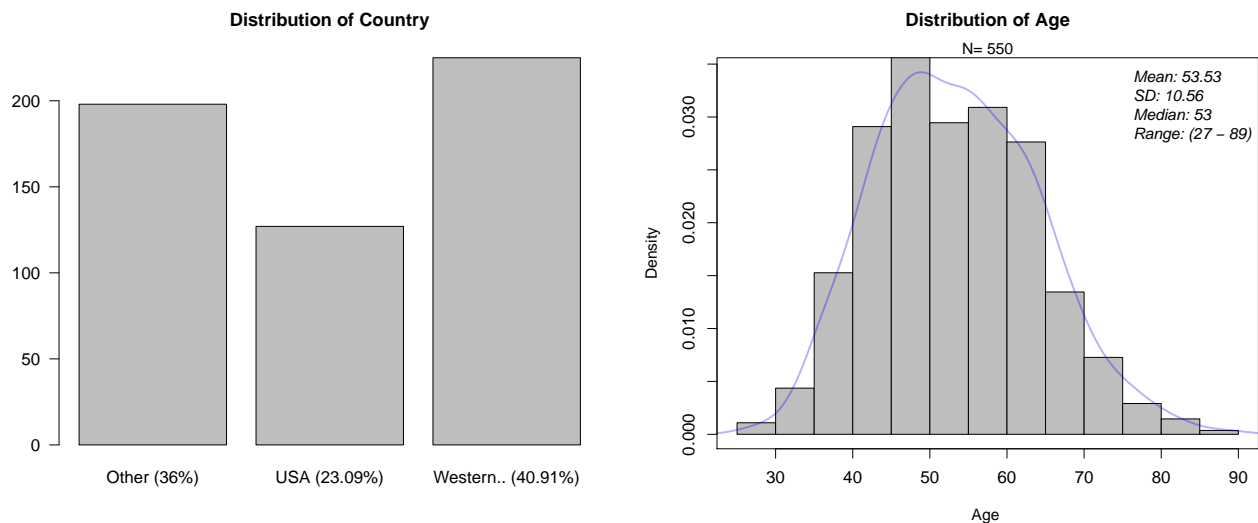
4.10 Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Plot only association between variables.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(mfrow=c(1,2), cex.axis=1.2),
show.biomarker.uni = FALSE)
```



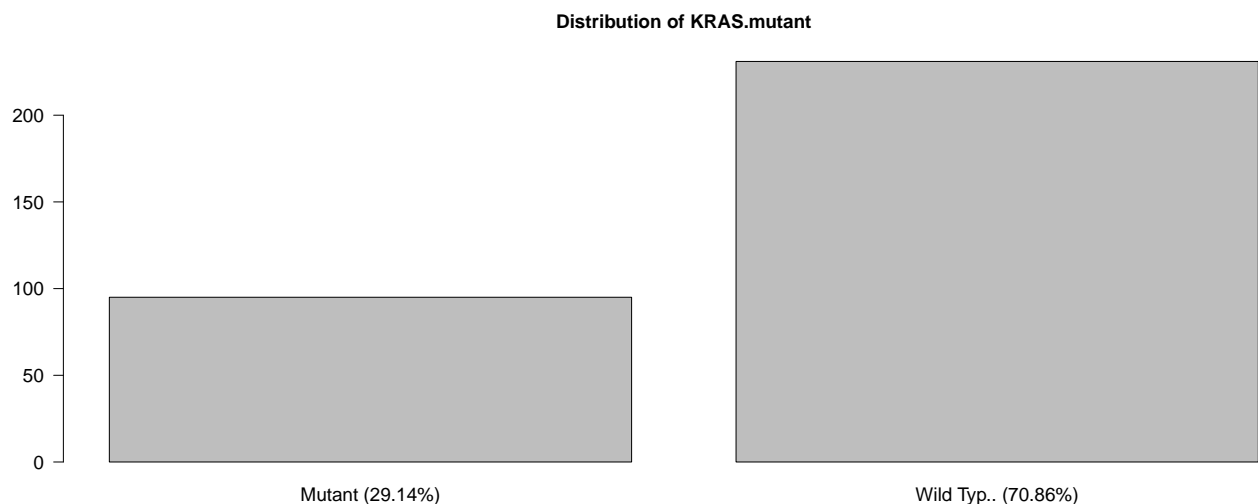
4.11 Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Plot only clinical variables.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(mfrow=c(1,2), cex.axis=1.1),
show.biomarker.uni = FALSE, show.association = FALSE,
show.clinical.uni = TRUE)
```



Categorical biomarker variable. Categorical and numeric clinical variables. No log transformation. Plot only biomarker variable.

```
PlotProperty(data=input, biomarker.var="KRAS.mutant", biomarker.class="categorical",
var=c("Country", "Age"), var.class=c("categorical", "numeric"),
par.param = list(cex.axis=1.2),
show.association = FALSE)
```

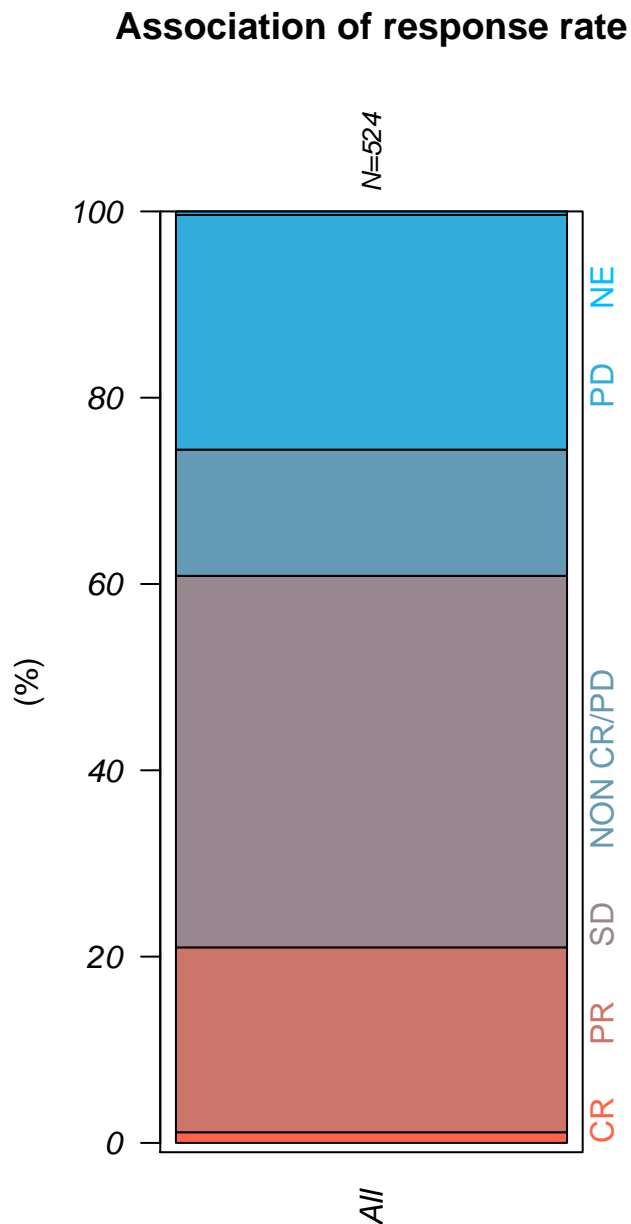


5 PlotRspBar(): Compare response outcome across different population

5.1 Plot response of one population

```
PlotRspBar (input, outcome.var="Response",  
            rsp.levels=c("CR", "PR", "SD", "NON CR/PD", "PD", "NE"))
```

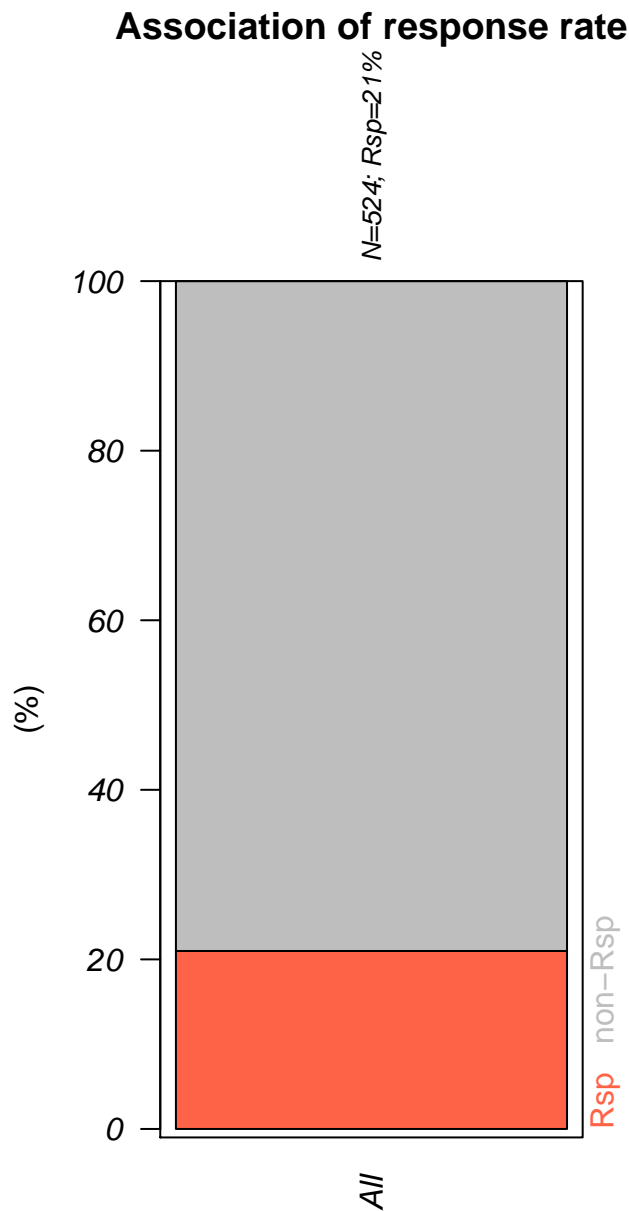
entries with missing outcome.var are removed! 524 entries left



5.2 Plot response of one population, binarize outcome (classify classes to responder vs non responder)

```
PlotRspBar (input, outcome.var="Response",  
            binary=TRUE,  
            rsp.response = c("CR","PR"),  
            rsp.nonresponse = c("SD", "PD", "NON CR/PD","NE",NA))
```

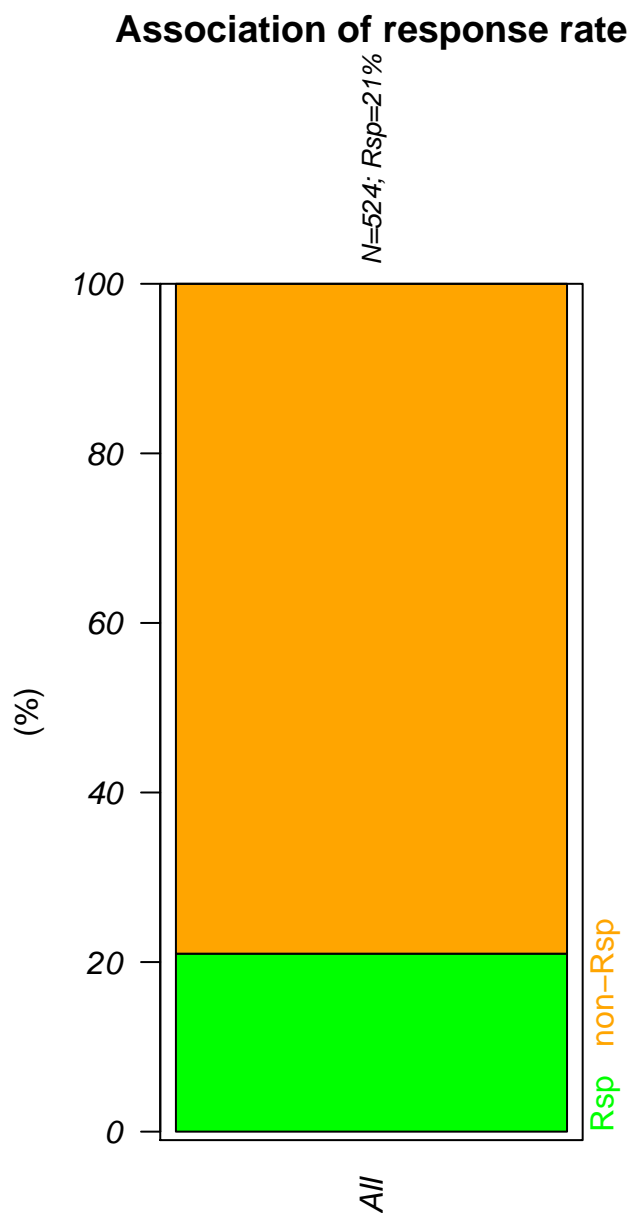
entries with missing outcome.var are removed! 524 entries left



5.3 Change color

```
PlotRspBar (input, outcome.var="Response",  
            binary=TRUE,  
            rsp.response = c("CR","PR"),  
            rsp.nonresponse = c("SD", "PD", "NON CR/PD", "NE", NA),  
            col=c("green","orange"))
```

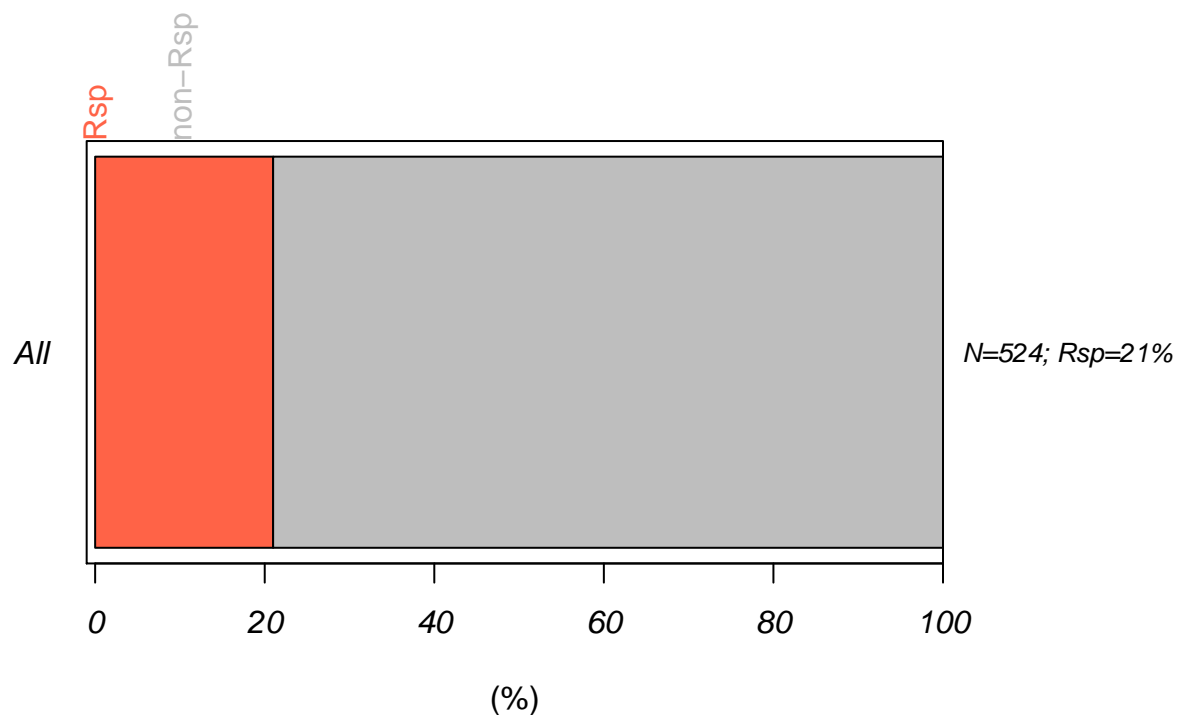
entries with missing outcome.var are removed! 524 entries left



5.4 Plot horizontally

```
PlotRspBar (input, outcome.var="Response",  
            binary=TRUE,  
            rsp.response = c("CR","PR"),  
            rsp.nonresponse = c("SD", "PD","NON CR/PD","NE",NA),  
            horiz=TRUE)
```

entries with missing outcome.var are removed! 524 entries left

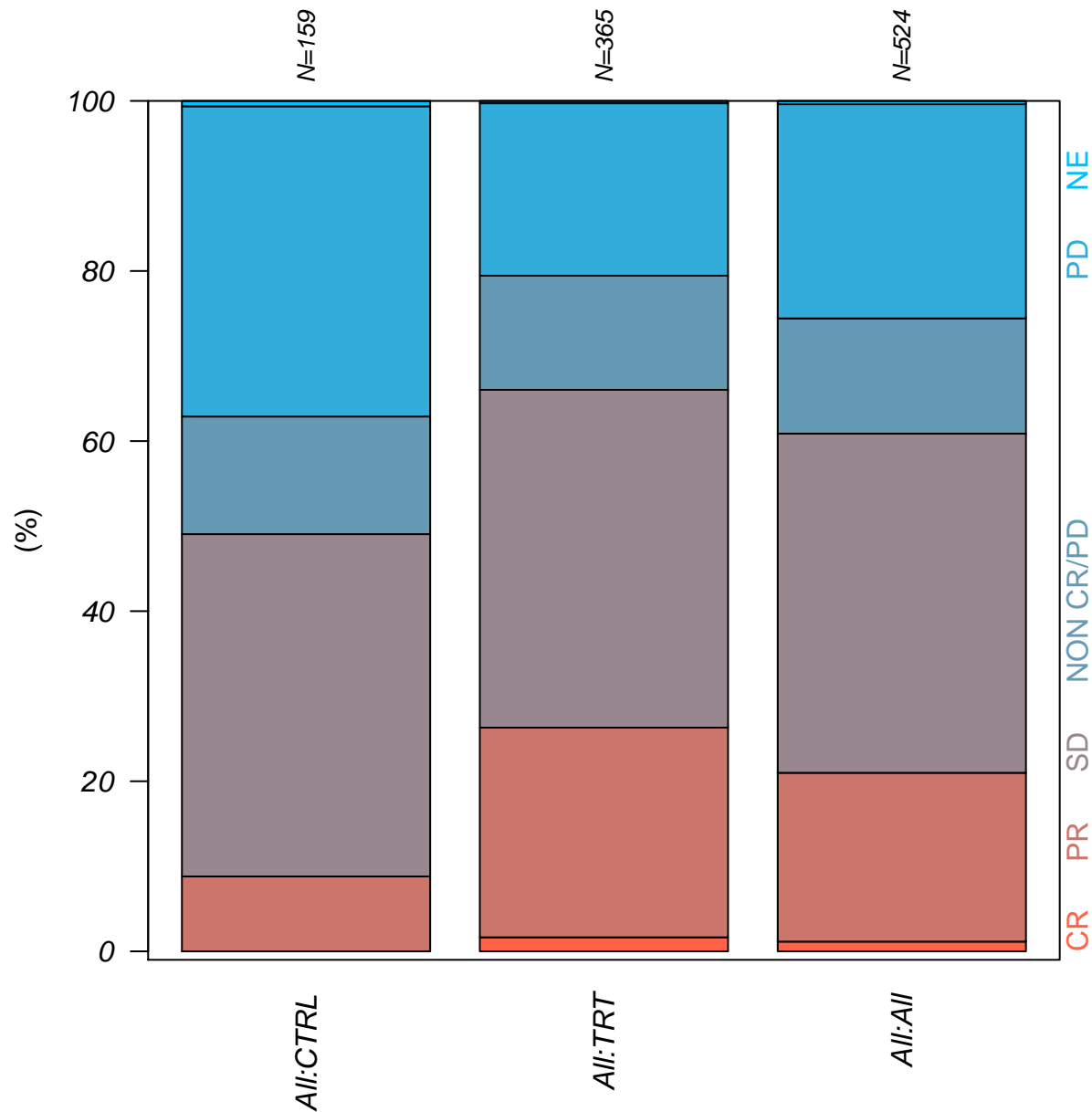


5.5 By arm

```
PlotRspBar (input, outcome.var="Response",  
            binary=FALSE,  
            rsp.levels=c("CR", "PR", "SD", "NON CR/PD", "PD", "NE"),  
            trt="Arm")
```

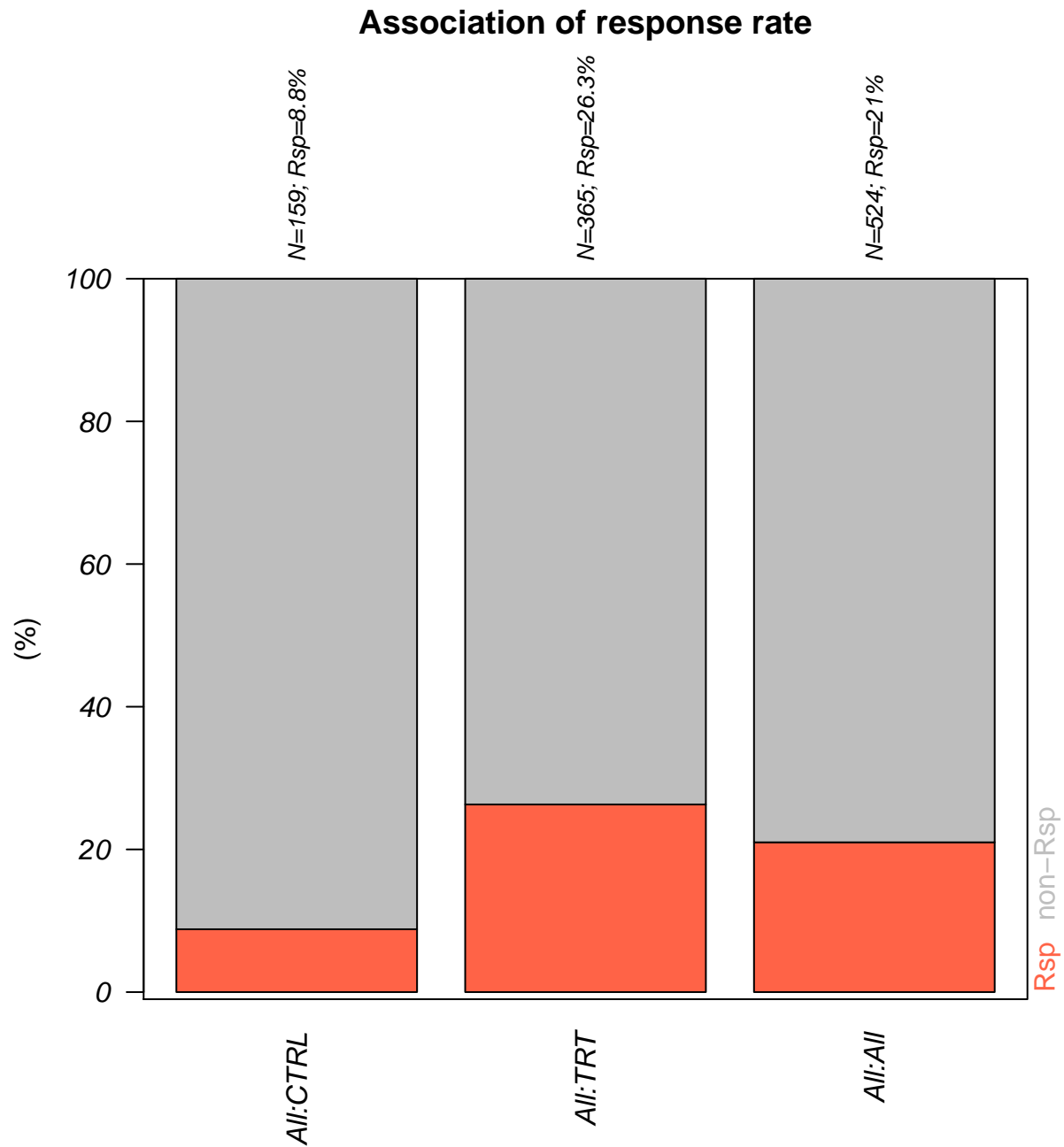
entries with missing outcome.var are removed! 524 entries left

Association of response rate



```
PlotRspBar (input, outcome.var="Response",
  binary=TRUE,
  rsp.response = c("CR", "PR"),
  rsp.nonresponse = c("SD", "PD", "NON CR/PD", "NE", NA),
  trt="Arm")
```

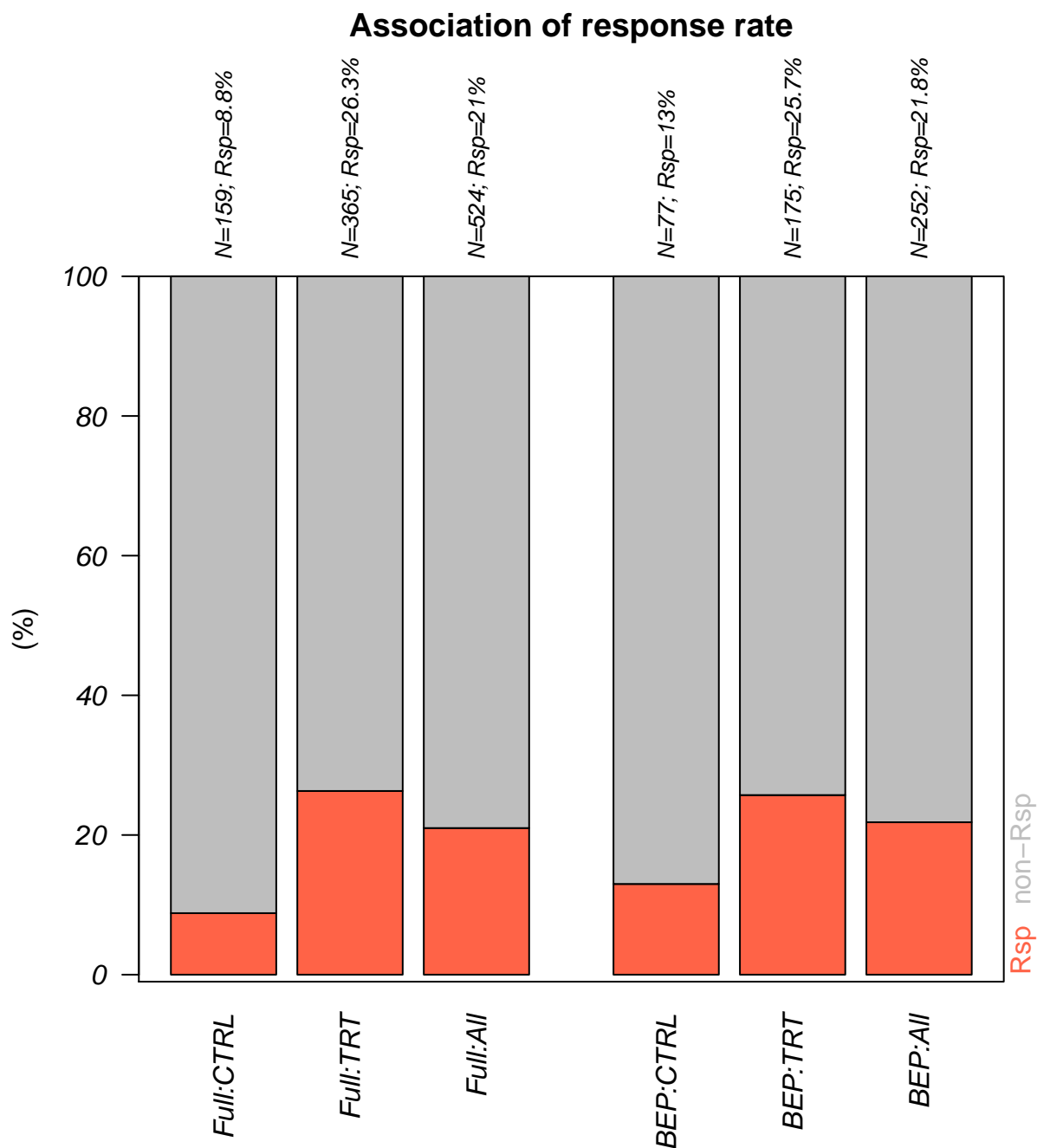
entries with missing outcome.var are removed! 524 entries left



5.6 Compare full population vs BEP

```
PlotRspBar (input, outcome.var="Response",
            binary=TRUE,
            rsp.response = c("CR", "PR"),
            rsp.nonresponse = c("SD", "PD", "NON CR/PD", "NE", NA),
            trt="Arm", compare.bep=TRUE, bep="BEP")
```

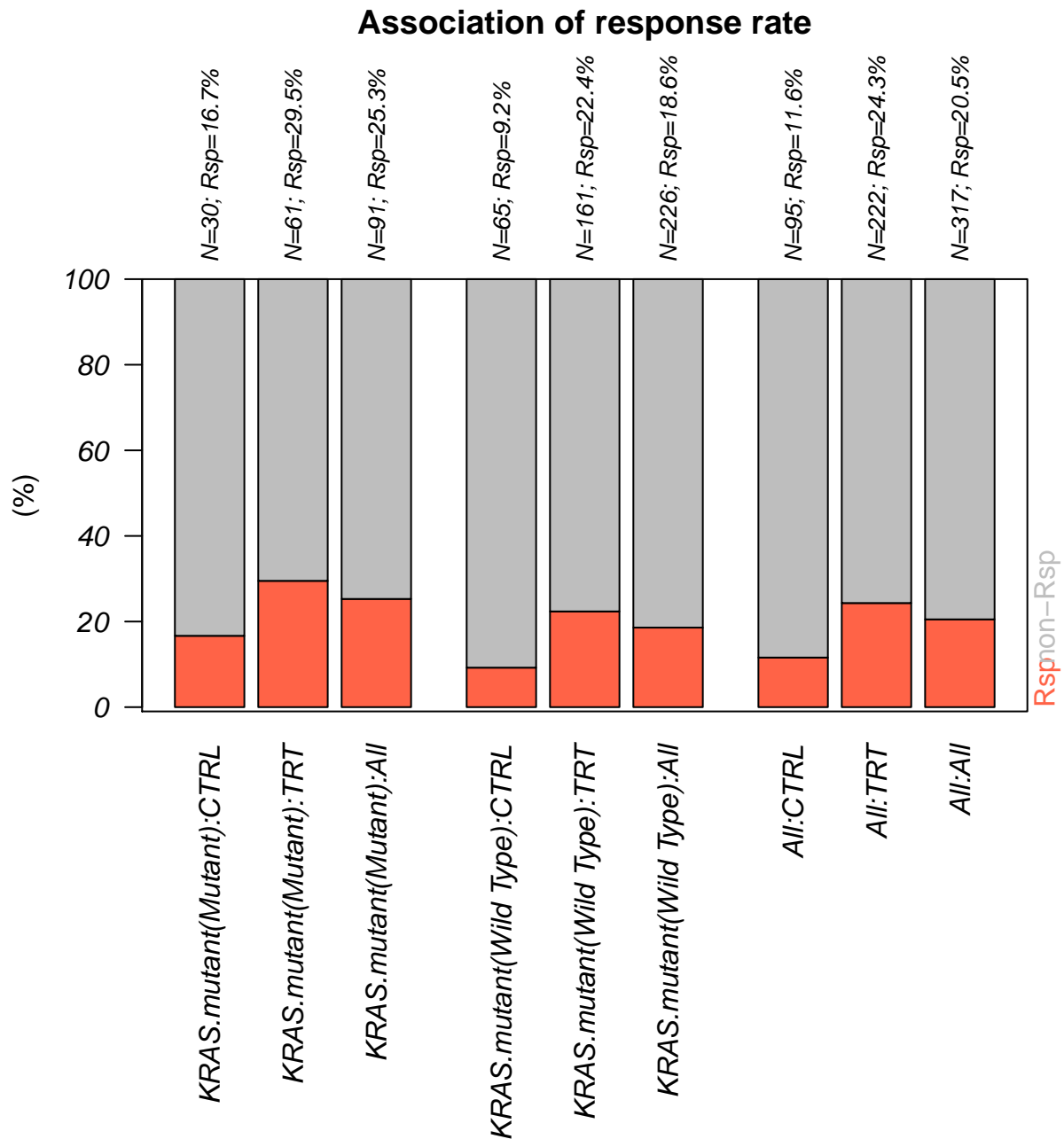
entries with missing outcome.var are removed! 524 entries left



5.7 Compare subgroups

```
PlotRspBar (input, outcome.var="Response",
            binary=TRUE,
            rsp.response = c("CR", "PR"),
            rsp.nonresponse = c("SD", "PD", "NON CR/PD", "NE", NA),
            trt="Arm", compare.var=TRUE, var="KRAS.mutant")
```

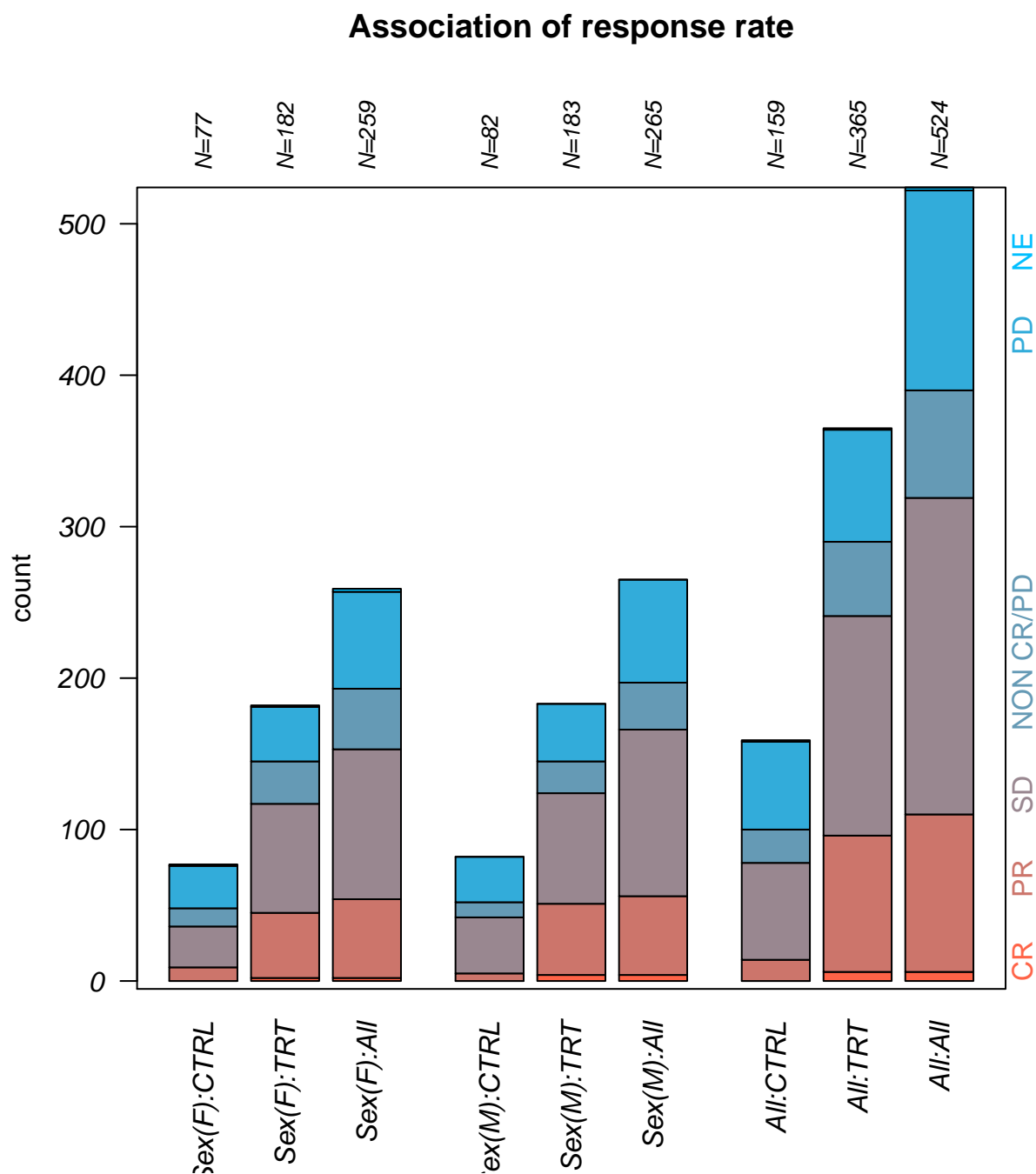
entries with missing outcome.var are removed! 524 entries left



5.8 Plot count instead of percentage

```
PlotRspBar (input, outcome.var="Response",
            binary=FALSE,
            rsp.levels=c("CR", "PR", "SD", "NON CR/PD", "PD", "NE"),
            trt="Arm",
            compare.var=TRUE, var="Sex", plot.count = TRUE)
```

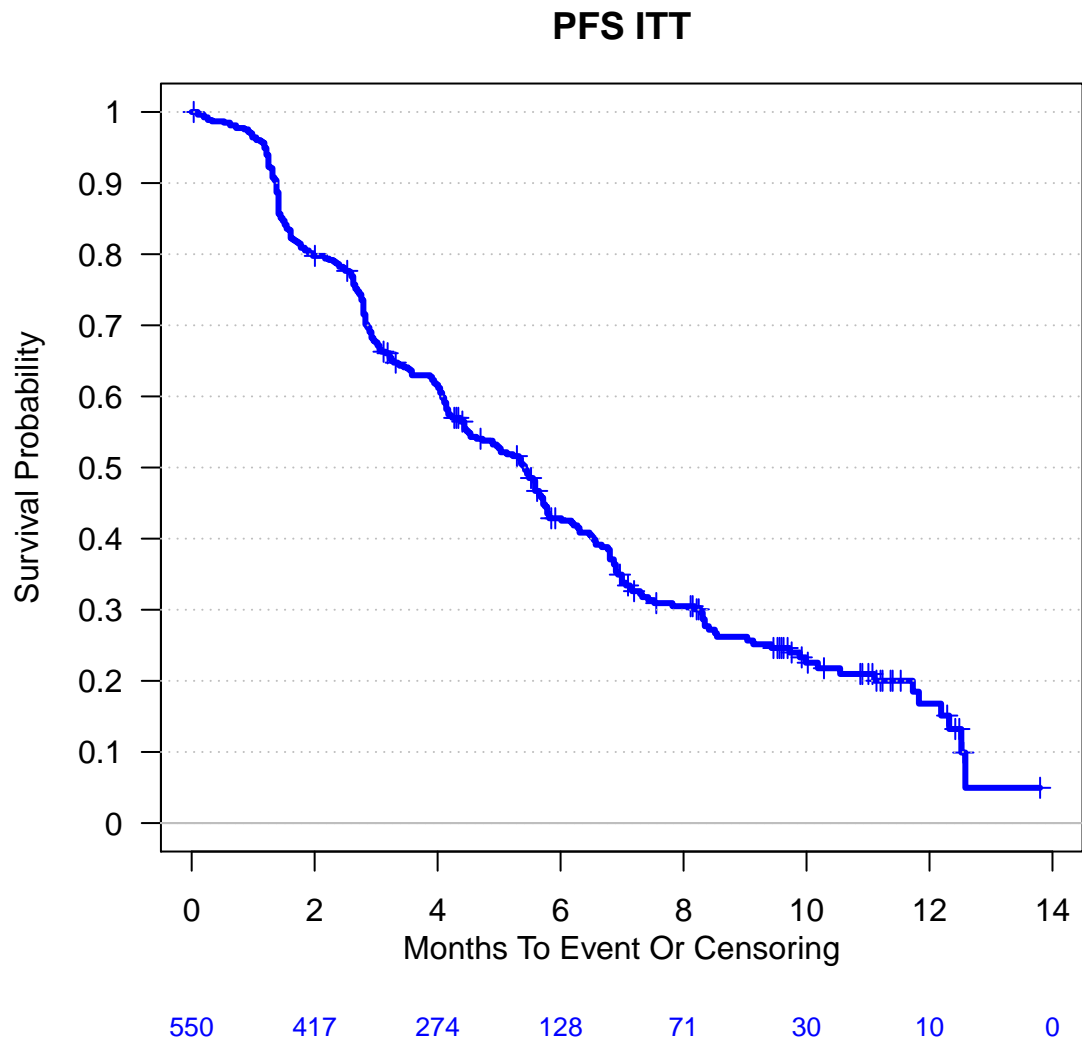
entries with missing outcome.var are removed! 524 entries left



6 PlotKM(): Plot KM curves for subpopulations

6.1 Without subgroup

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
             main="PFS ITT"))
```

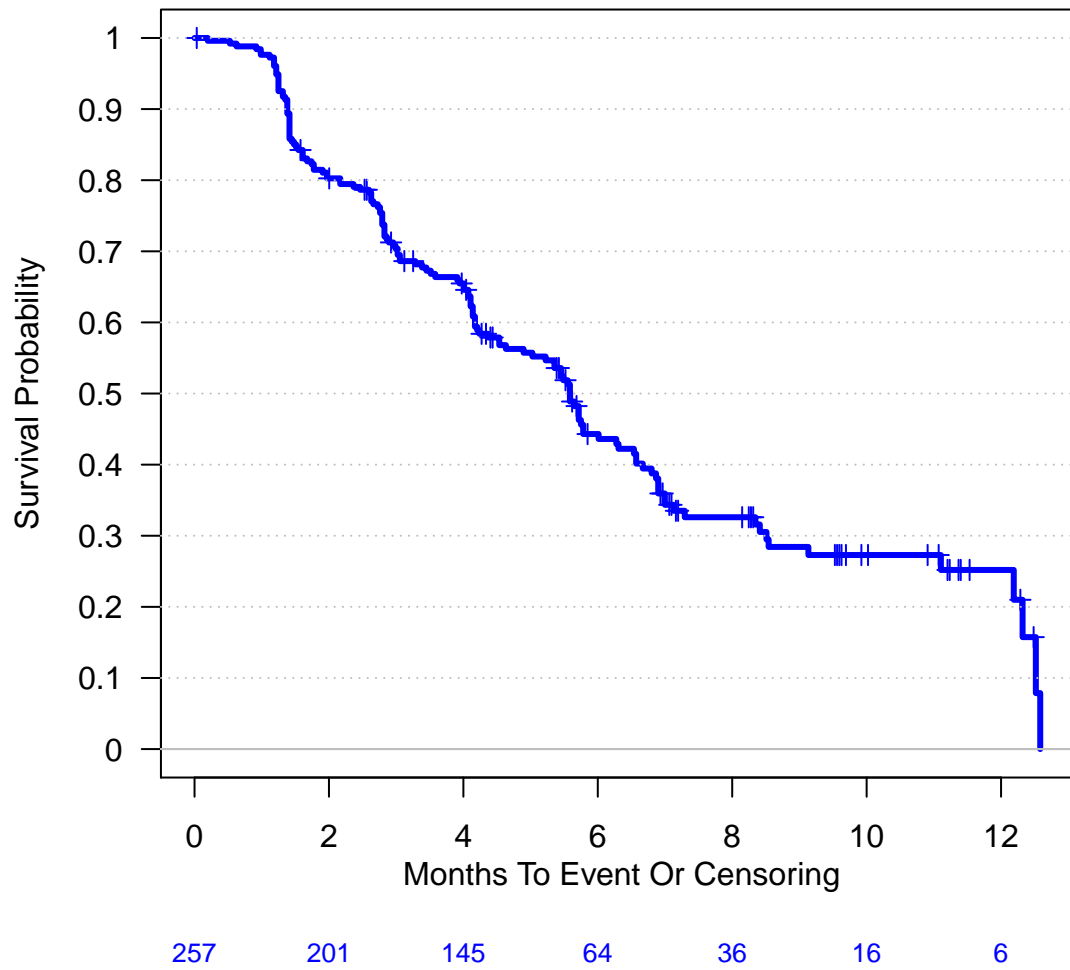


```
## [1] ""
```

6.2 Without subgroup, BEP

```
print(PlotKM(data=sample.data, bep="BEP",
             tte="PFS", cen="PFS.event", main="PFS BEP"))
```

PFS BEP

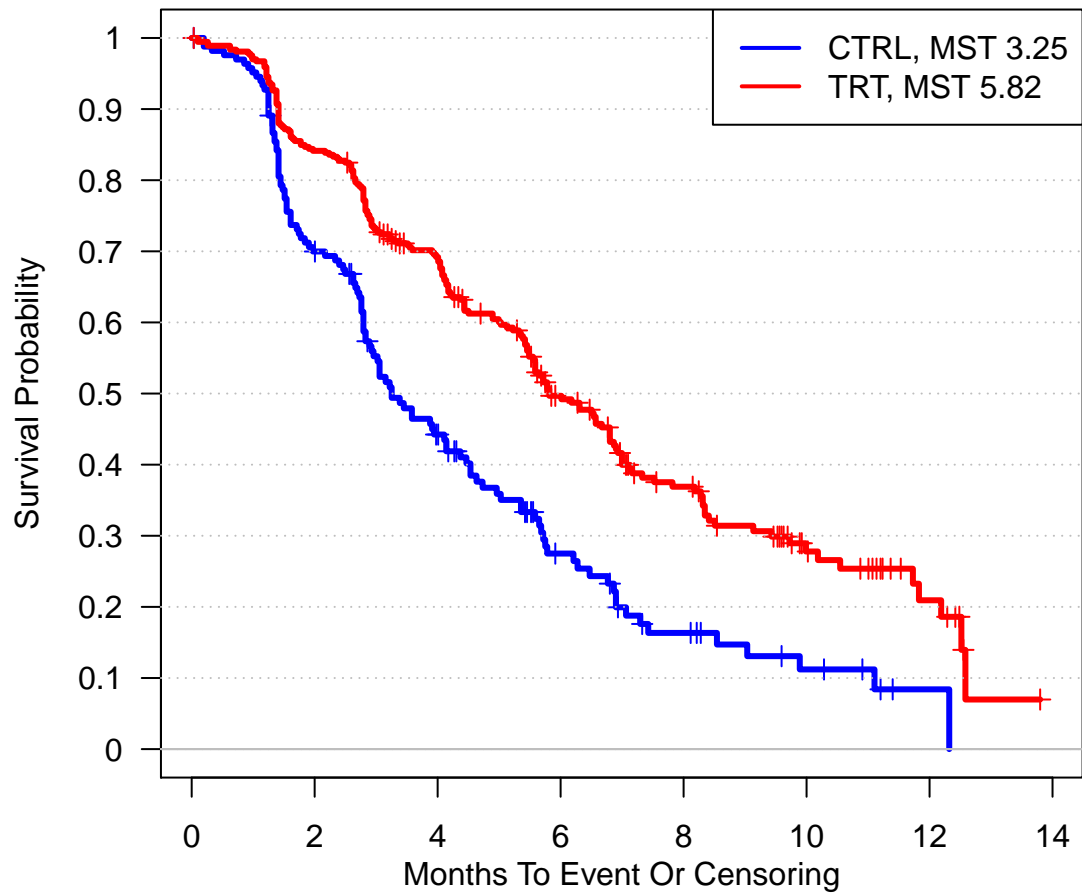


```
## [1] ""
```

6.3 By TRT

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",  
             main="PFS ITT by treatment", trt="Arm"))
```

PFS ITT by treatment

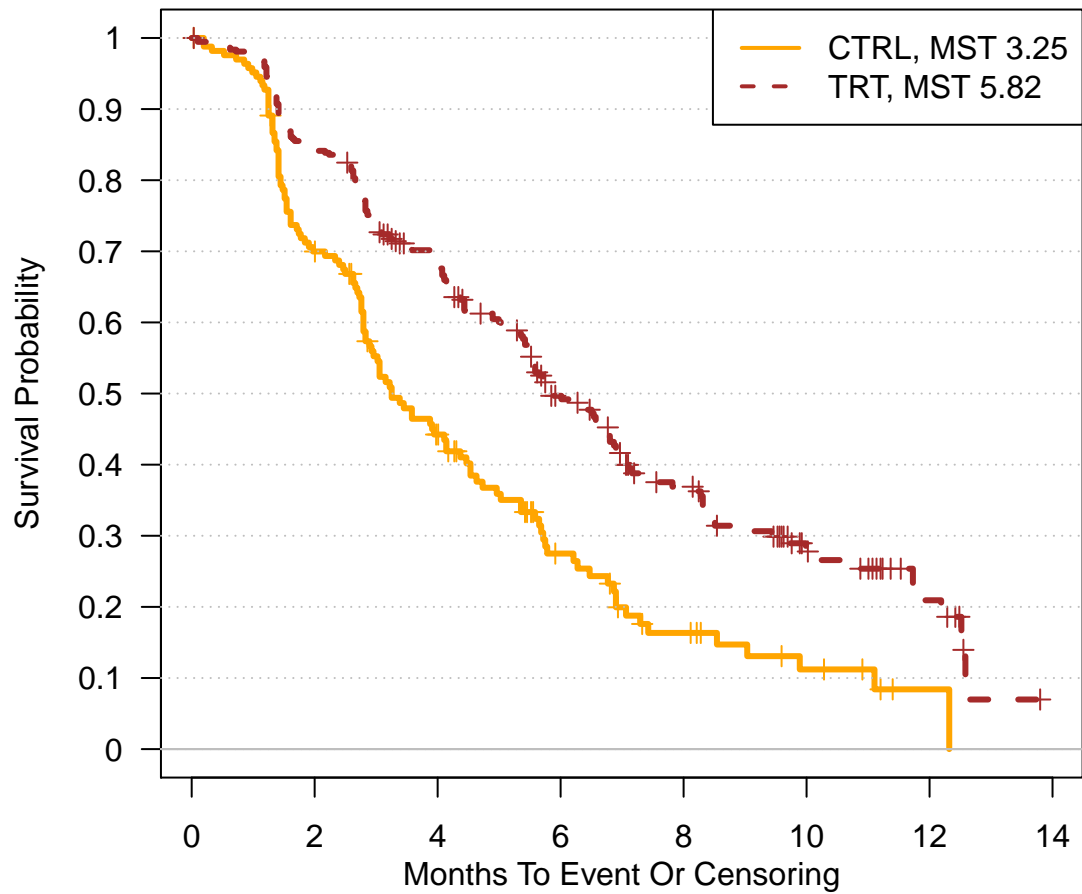


```
## [1] ""
```

6.4 By TRT, change color, line type

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
             main="PFS ITT by treatment", trt="Arm",
             col=c("orange", "brown"), lty=c(1,2)))
```

PFS ITT by treatment



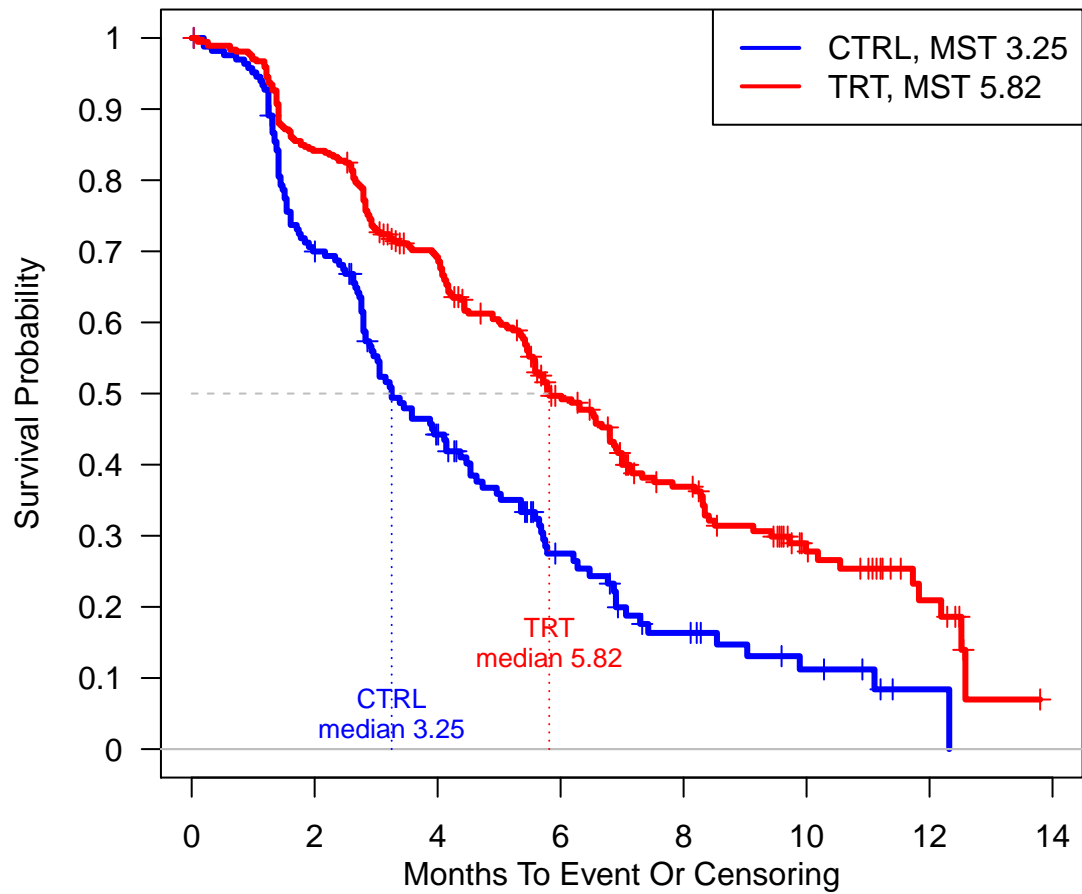
CTRL	182	112	58	26	13	6	1	0
TRT	368	305	216	102	58	24	9	0

```
## [1] ""
```

6.5 Mark median PFS, no grid

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
             main="PFS ITT by treatment",
             trt="Arm",
             plot.grid = FALSE,
             plot.median=T))
```

PFS ITT by treatment



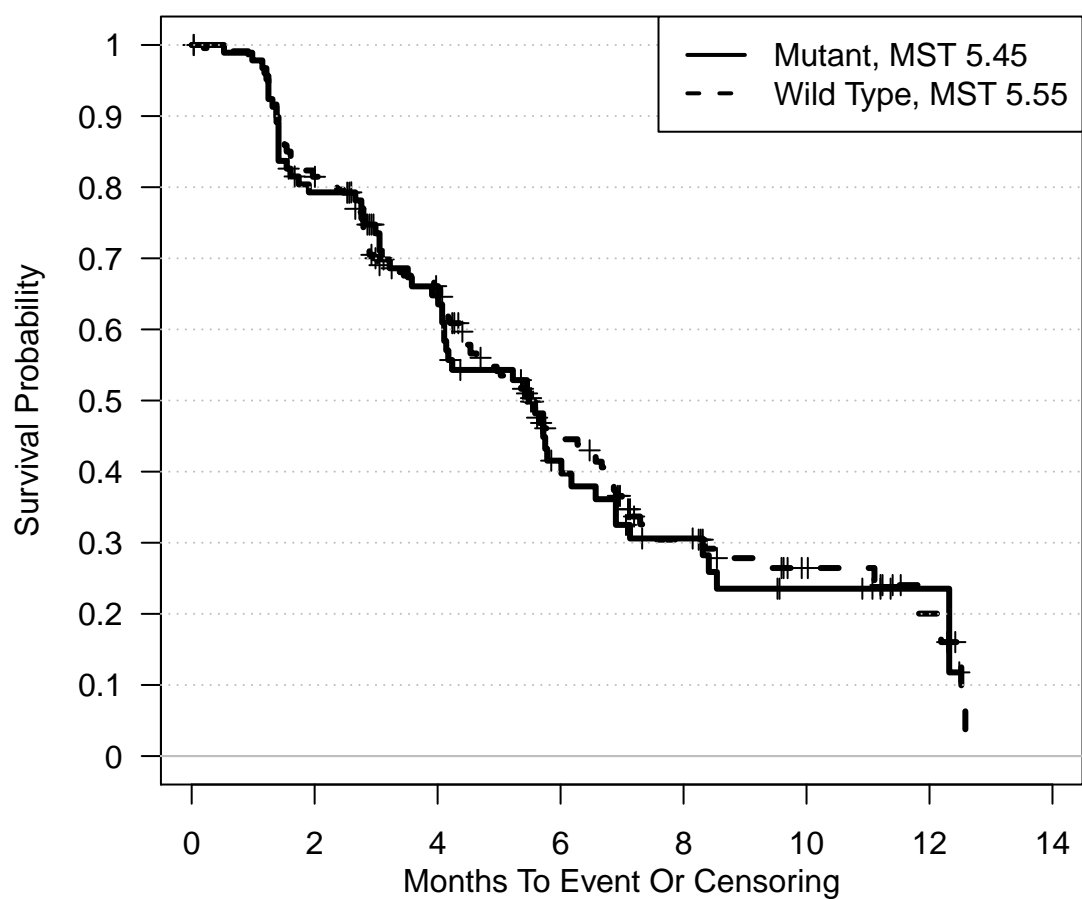
CTRL	182	112	58	26	13	6	1	0
TRT	368	305	216	102	58	24	9	0

[1] ""

6.6 By KRAS.mutant only

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
             main="OS BEP by treatment, by KRAS mutation",
             var="KRAS.mutant"))
```


OS BEP by treatment, by KRAS mutation

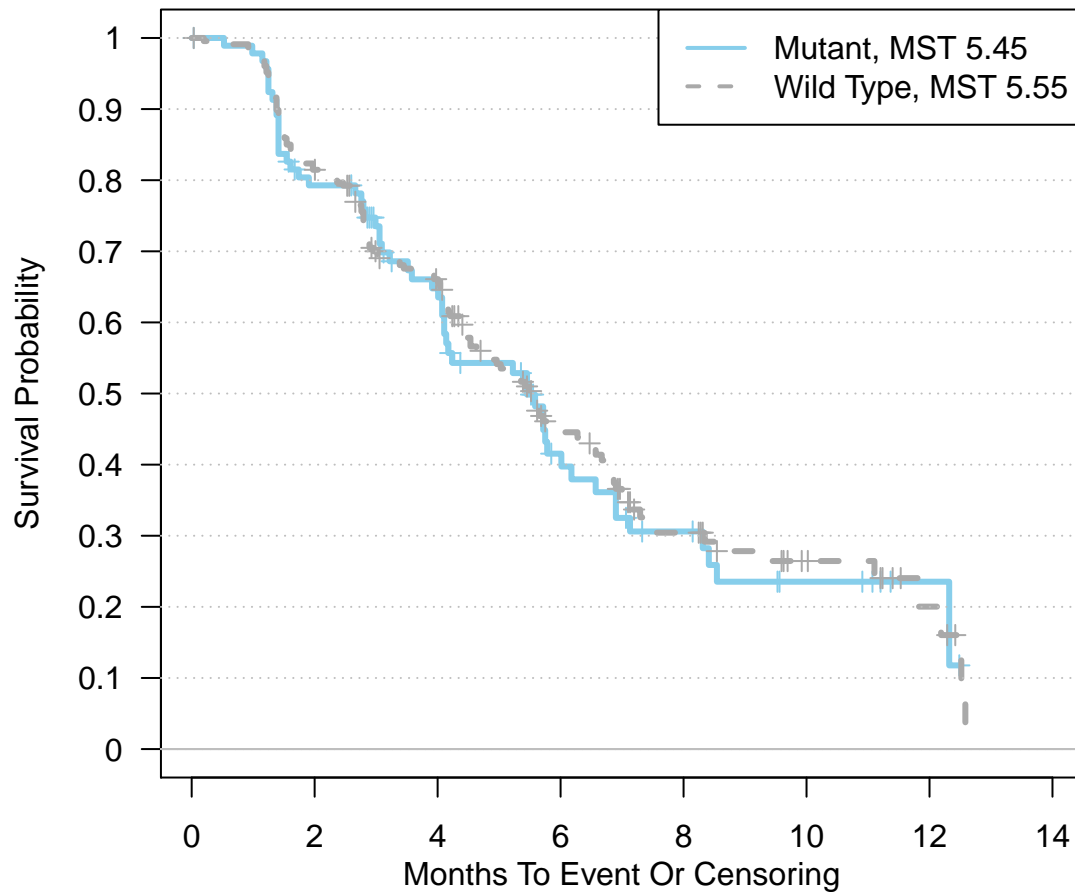


Mutant	95	71	51	23	14	7	2	0
Wild Type	231	183	133	57	28	12	5	0

```
## [1] ""
```

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="OS BEP by treatment, by KRAS mutation",
  var="KRAS.mutant", col=c("skyblue", "darkgray")))
```

OS BEP by treatment, by KRAS mutation



Mutant	95	71	51	23	14	7	2	0
Wild Type	231	183	133	57	28	12	5	0

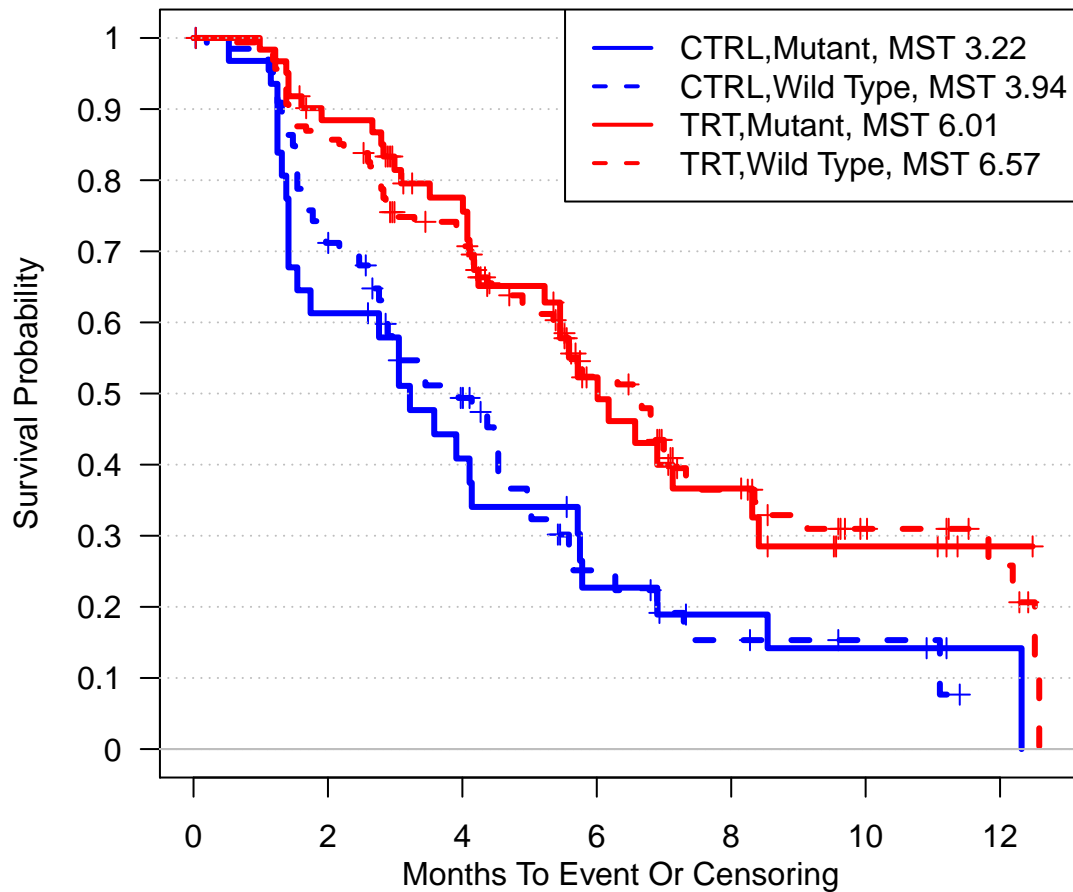
```
## [1] ""
```

6.7 By TRT and KRAS.mutant

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="OS BEP by treatment, by KRAS mutation",
  trt="Arm", var="KRAS.mutant"))
```

```
## entries who have NA in trt, var, or varlist are removed
```

OS BEP by treatment, by KRAS mutation



CTRL, Mutant	34	19	12	6	4	3	1
CTRL, Wild Type	69	46	27	9	4	2	0
TRT, Mutant	61	52	39	17	10	4	1
TRT, Wild Type	162	137	106	48	24	10	5

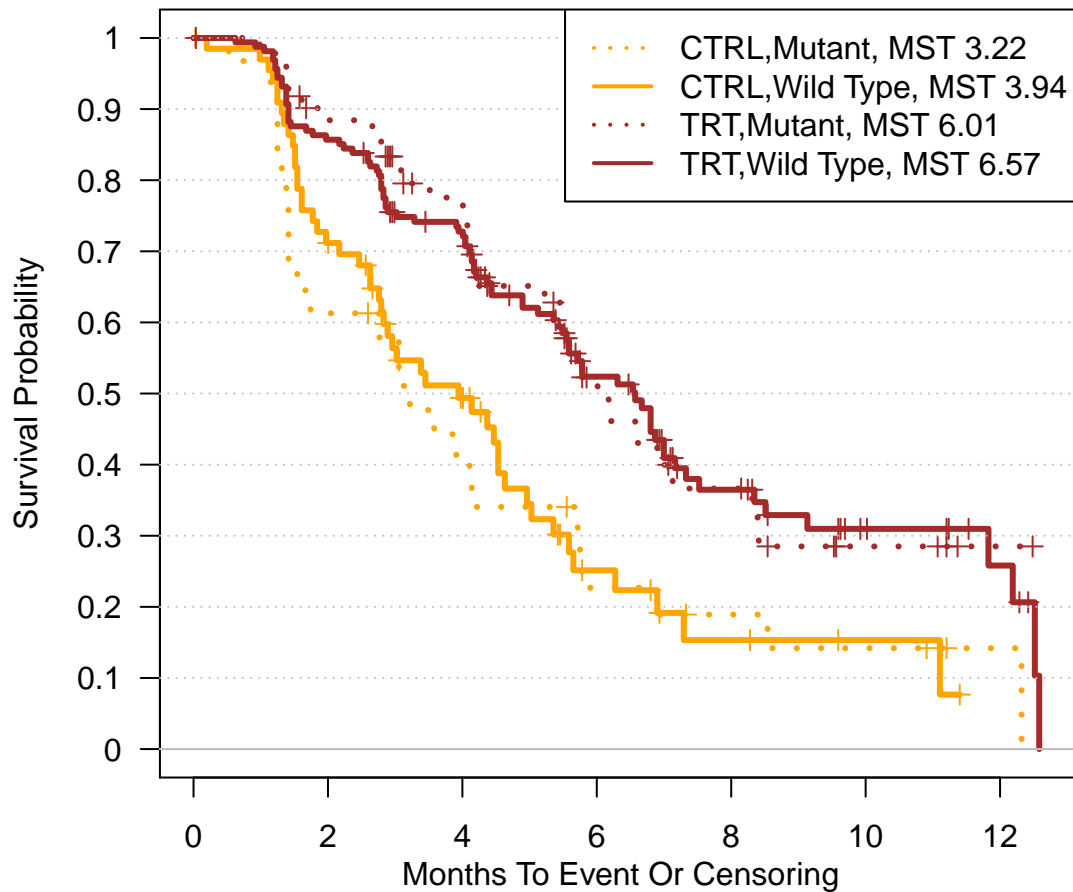
```
## [1] ""
```

6.8 By TRT and KRAS.mutant, change color and line type

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="PFS BEP by treatment, by KRAS mutation",
  trt="Arm", var="KRAS.mutant",
  col=c("orange", "orange", "brown", "brown"),
  lty=c(3, 1, 3, 1)))
```

```
## entries who have NA in trt, var, or varlist are removed
```

PFS BEP by treatment, by KRAS mutation



CTRL, Mutant	34	19	12	6	4	3	1
CTRL, Wild Type	69	46	27	9	4	2	0
TRT, Mutant	61	52	39	17	10	4	1
TRT, Wild Type	162	137	106	48	24	10	5

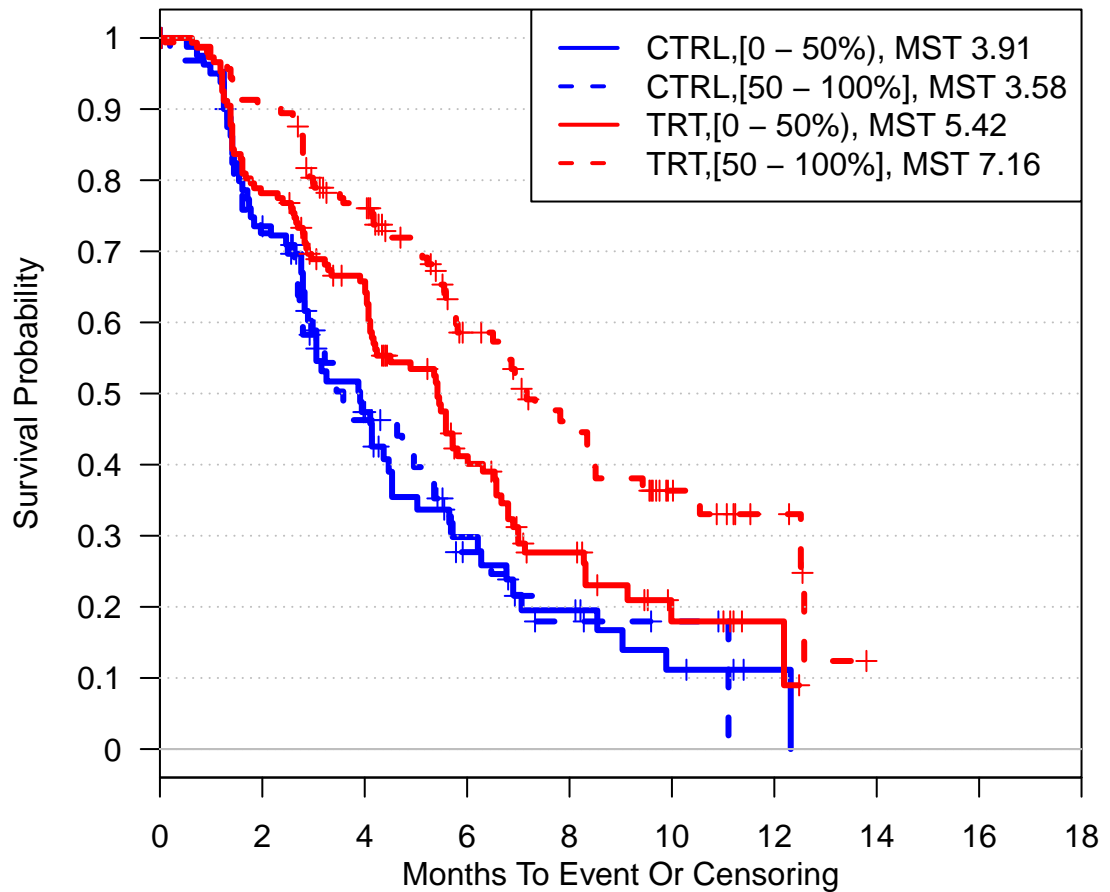
```
## [1] ""
```

6.9 By TRT and KRAS.expression (continuous biomarker, cut at median)

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="PFS BEP by treatment, by KRAS expression",
  trt="Arm", var="KRAS.exprs", var.class="numeric",
  percentile.cutoff=0.5, xlim=c(0,18))
)
```

```
## entries who have NA in trt, var, or varlist are removed
```

PFS BEP by treatment, by KRAS expression



CTRL,[0 - 50%)	82	58	31	15	9	4	1	0	0	0
CTRL,[50 - 100%)	70	44	23	9	4	2	0	0	0	0
TRT,[0 - 50%)	147	113	83	38	20	6	2	0	0	0
TRT,[50 - 100%)	162	145	105	47	30	12	5	0	0	0

0%: 1.42. 50%: 70.52. 100%: 9541.5.

[1] ""

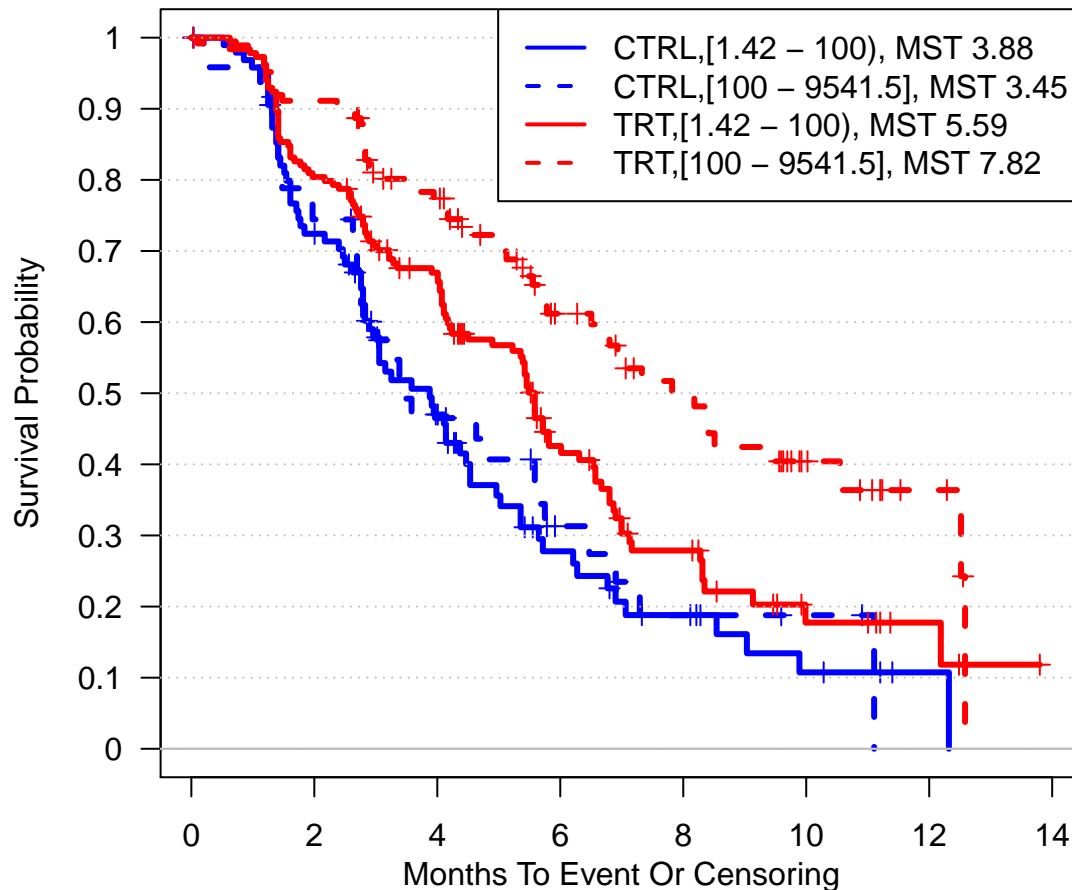
6.10 By TRT and KRAS.expression (continuous biomarker, cut at a numerical cutoff)

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="PFS BEP by treatment, by KRAS expression",
  trt="Arm", var="KRAS.exprs", var.class="numeric",
  numerical.cutoff=100)
)
```

```
## numerical cutoff specified
```

```
## entries who have NA in trt, var, or varlist are removed
```

PFS BEP by treatment, by KRAS expression



CTRL,[1.42 - 100)	99	68	37	16	9	4	1	0
CTRL,[100 - 9541.5]	53	34	17	8	4	2	0	0
TRT,[1.42 - 100)	184	146	104	43	22	7	3	0
TRT,[100 - 9541.5]	125	112	84	42	28	11	4	0

```
## [1] ""
```

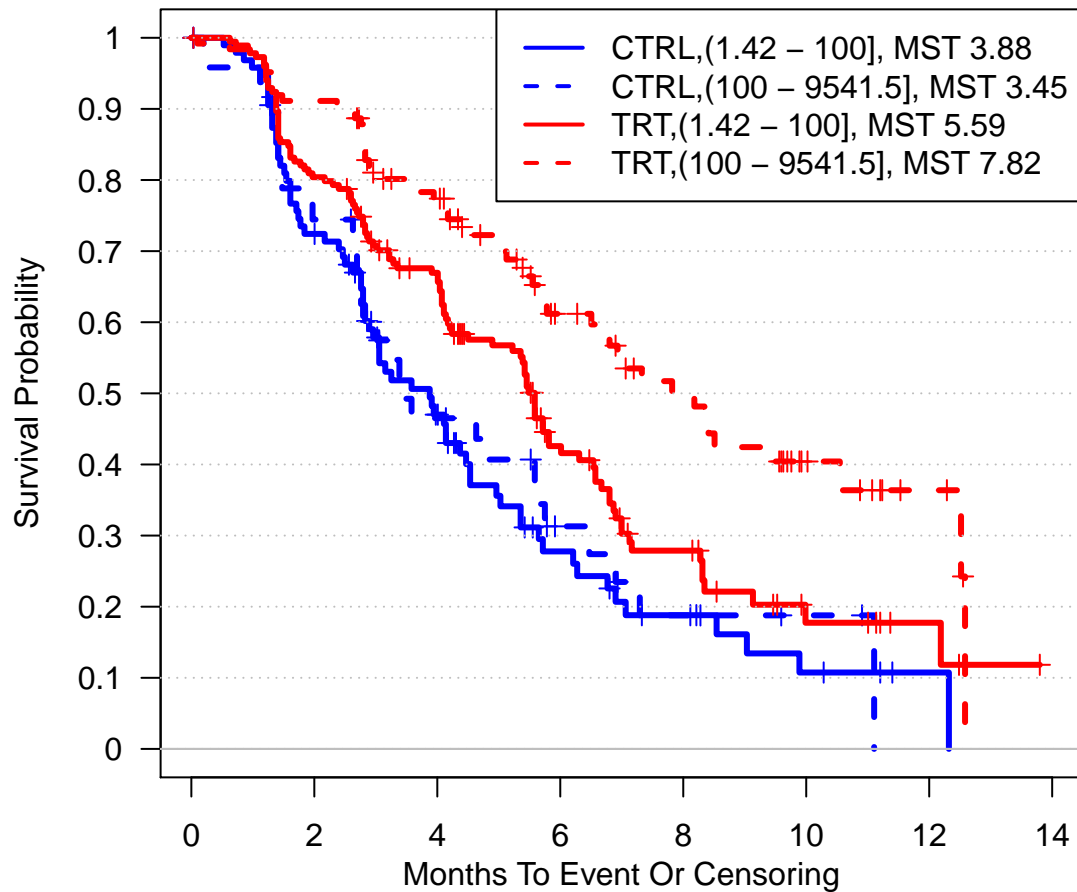
6.11 By TRT and KRAS.expression (continuous biomarker, cut at a numerical cutoff). High group defined as “greater than”, instead of “greater than or equal to”

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="PFS BEP by treatment, by KRAS expression",
  trt="Arm", var="KRAS.exprs", var.class="numeric",
  numerical.cutoff=100, equal.in.high = F)
)
```

```
## numerical cutoff specified
```

```
## entries who have NA in trt, var, or varlist are removed
```

PFS BEP by treatment, by KRAS expression



CTRL,(1.42 - 100]	99	68	37	16	9	4	1	0
CTRL,(100 - 9541.5]	53	34	17	8	4	2	0	0
TRT,(1.42 - 100]	184	146	104	43	22	7	3	0
TRT,(100 - 9541.5]	125	112	84	42	28	11	4	0

```
## [1] ""
```

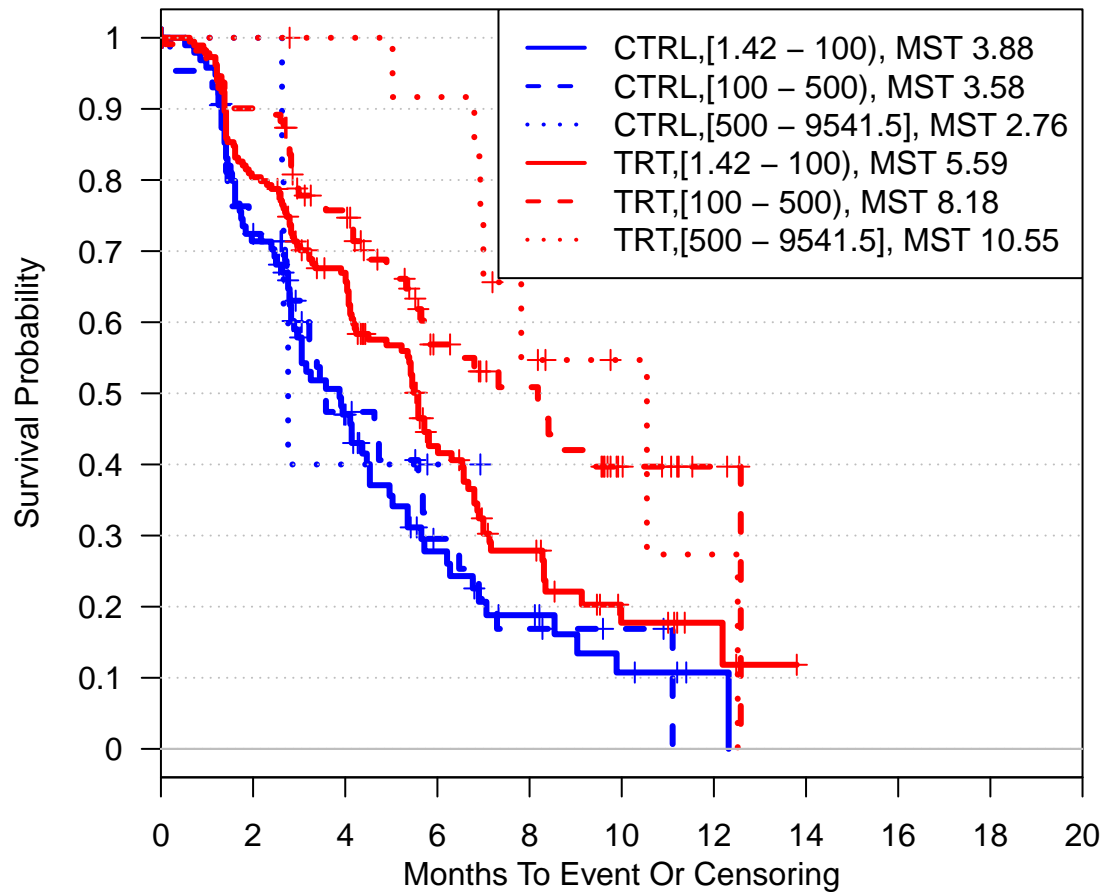
6.12 By TRT and KRAS.expression , more than 2 groups

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="PFS BEP by treatment, by KRAS expression",
  trt="Arm", var="KRAS.exprs", var.class="numeric",
  numerical.cutoff=c(100,500), xlim=c(0, 20))
)
```

```
## numerical cutoff specified
```

```
## entries who have NA in trt, var, or varlist are removed
```

PFS BEP by treatment, by KRAS expression



CTRL,[1.42 - 100)	99	68	37	16	9	4	1	0	0	0	0
CTRL,[100 - 500)	47	29	15	7	4	2	0	0	0	0	0
CTRL,[500 - 9541.5]	6	5	2	1	0	0	0	0	0	0	0
TRT,[1.42 - 100)	184	146	104	43	22	7	3	0	0	0	0
TRT,[100 - 500)	112	99	72	31	23	9	3	0	0	0	0
TRT,[500 - 9541.5]	13	13	12	11	5	2	1	0	0	0	0

```
## [1] ""
```

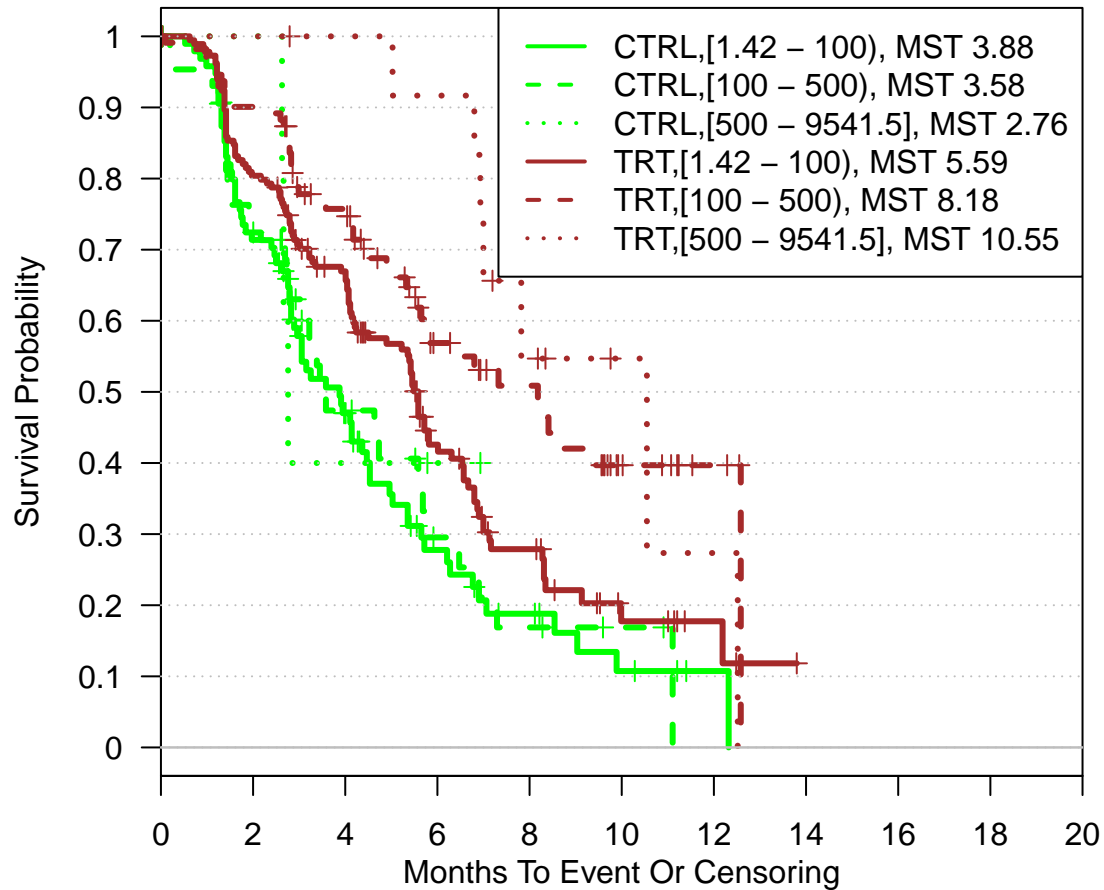
```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  main="PFS BEP by treatment, by KRAS expression",
  trt="Arm", var="KRAS.exprs", var.class="numeric",
  numerical.cutoff=c(100,500),
  col=c("green", "green", "green", "brown", "brown", "brown"),
  xlim=c(0,20))
)
```



```
## numerical cutoff specified
```

```
## entries who have NA in trt, var, or varlist are removed
```

PFS BEP by treatment, by KRAS expression



CTRL,[1.42 – 100)	99	68	37	16	9	4	1	0	0	0	0
CTRL,[100 – 500)	47	29	15	7	4	2	0	0	0	0	0
CTRL,[500 – 9541.5]	6	5	2	1	0	0	0	0	0	0	0
TRT,[1.42 – 100)	184	146	104	43	22	7	3	0	0	0	0
TRT,[100 – 500)	112	99	72	31	23	9	3	0	0	0	0
TRT,[500 – 9541.5]	13	13	12	11	5	2	1	0	0	0	0

```
## [1] ""
```

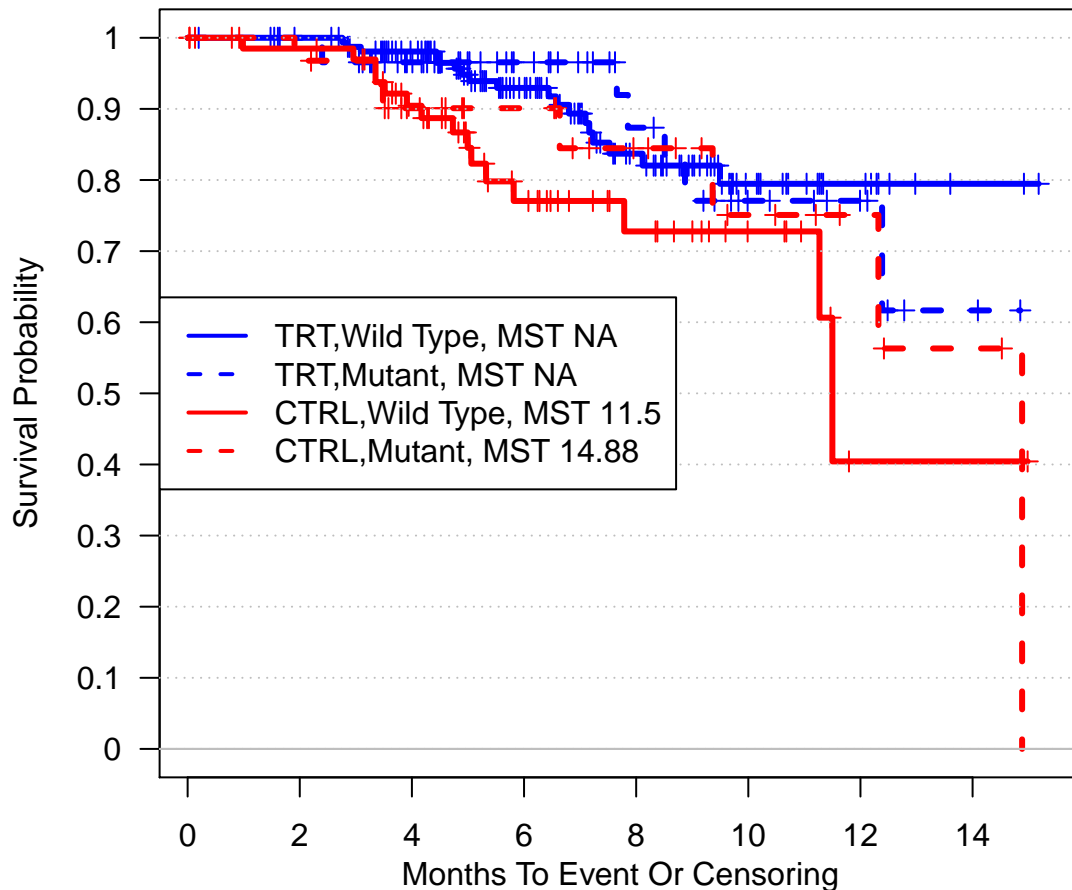
6.13 More flexibility, reorder subgroups

```
print(PlotKM(data=sample.data, tte="OS", cen="OS.event",
  main="OS BEP by treatment, by KRAS mutation",
  varlist=c("Arm", "KRAS.mutant"),
  varlist.levels=list(c("TRT", "CTRL"), c("Wild Type", "Mutant")),
  legend.loc="left"))
```

```
## 'varlist' is specified, trt and var parameters will be ignored
```

```
## entries who have NA in trt, var, or varlist are removed
```

OS BEP by treatment, by KRAS mutation



TRT, Wild Type	162	159	137	87	50	22	10	2
TRT, Mutant	61	58	48	31	19	10	6	2
CTRL, Wild Type	69	65	52	28	17	9	1	1
CTRL, Mutant	34	30	23	18	12	7	4	2

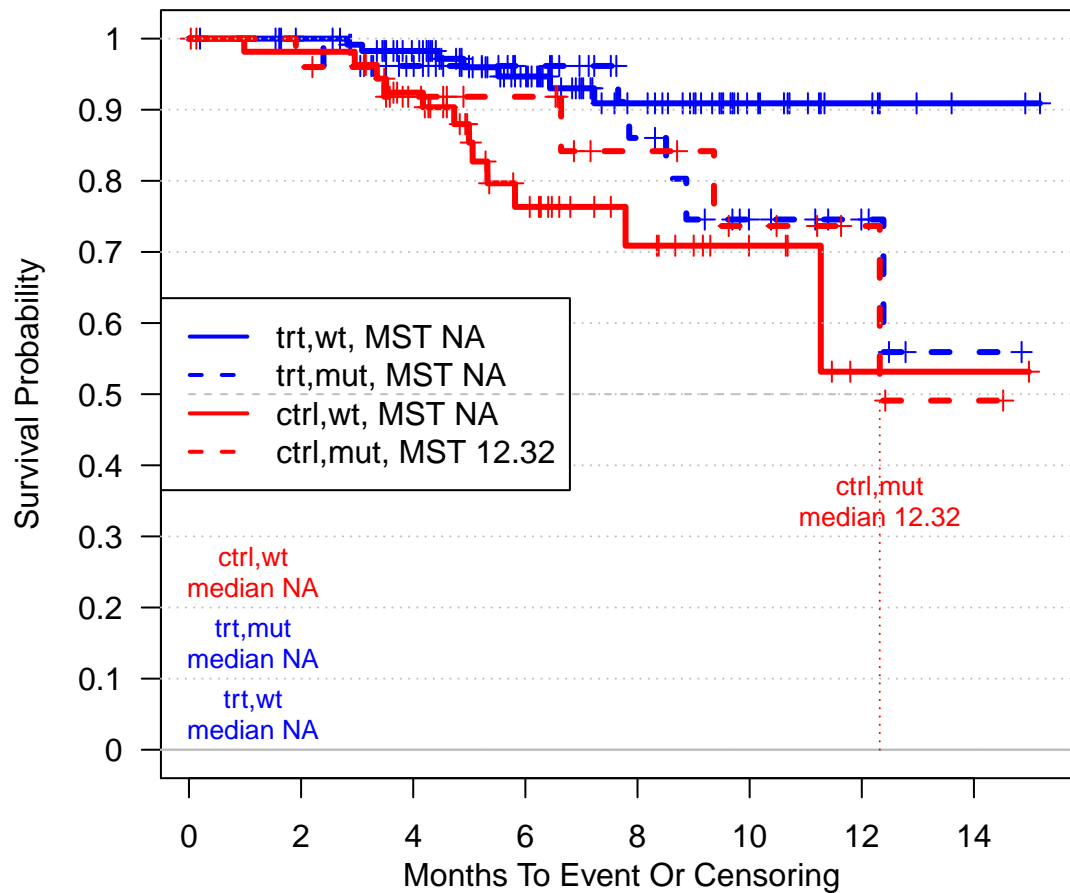
```
## [1] ""
```

6.14 By TRT and KRAS.mutant, reorder and rename

```
print(PlotKM(data=sample.data, tte="OS", cen="OS.event", bep="BEP",
  main="OS BEP by treatment, by KRAS mutation", varlist=c("Arm", "KRAS.mutant"),
  varlist.levels=list(c("TRT", "CTRL"), c("Wild Type", "Mutant")),
  varlist.labels=list(c("trt", "ctrl"), c("wt", "mut")),
  plot.median=T, legend.loc="left"))
```

```
## 'varlist' is specified, trt and var parameters will be ignored
```

OS BEP by treatment, by KRAS mutation



trt,wt	121	119	101	66	38	17	7	2
trt,mut	55	52	43	28	17	9	5	1
ctrl,wt	56	53	45	23	13	6	1	1
ctrl,mut	25	24	18	14	9	6	3	1

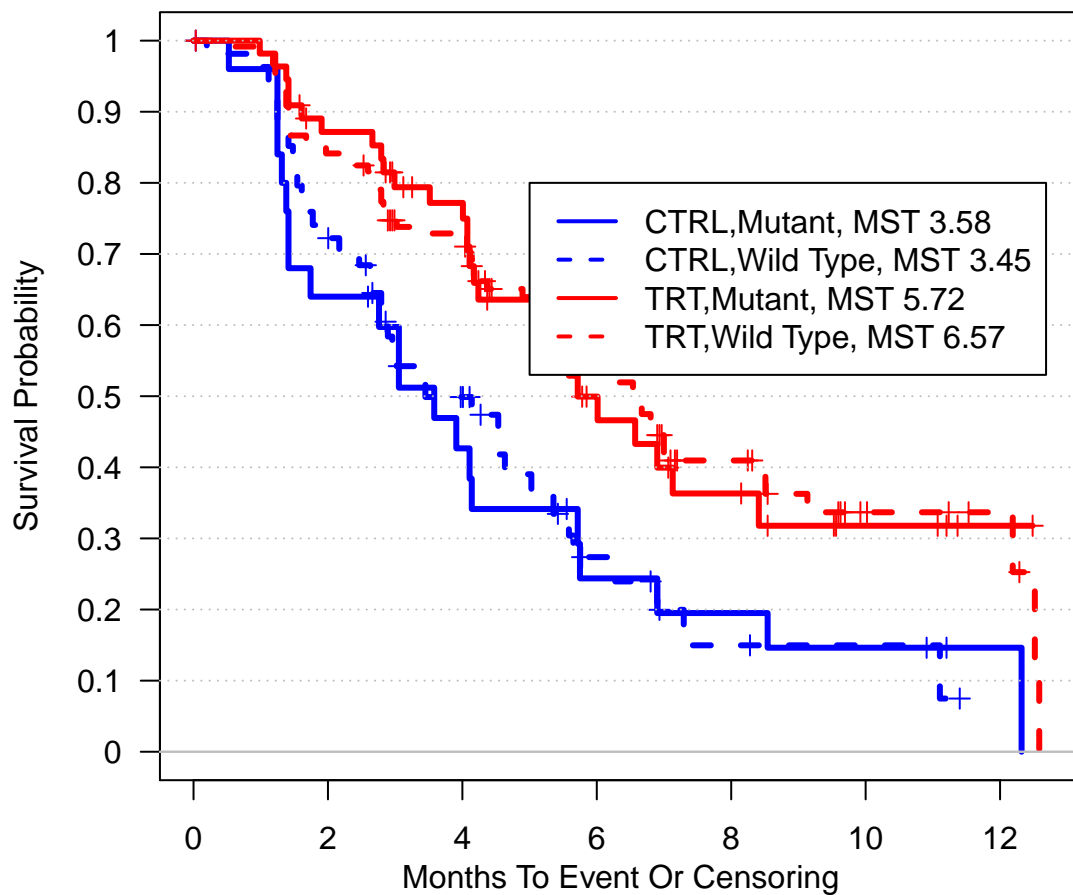
```
## [1] ""
```

6.15 Legend location

```
print(PlotKM(data=sample.data, tte="PFS", cen="PFS.event",
  var=c("Arm", "KRAS.mutant"),
  bep="BEP", legend.loc=NULL, legend.x=5, legend.y=.8))
```

```
## more than one elements in 'var', trt parameter will be ignored
```

```
## 'varlist' is specified, trt and var parameters will be ignored
```



CTRL,Mutant	25	16	10	5	4	3	1
CTRL,Wild Type	56	39	22	8	3	2	0
TRT,Mutant	55	46	35	15	9	4	1
TRT,Wild Type	121	100	78	36	20	7	4

```
## [1] ""
```

7 PlotTabForestBiomarker() : forest plot and summary statistics table for a single biomarker (include cutoff exploration for cont. biomarker)

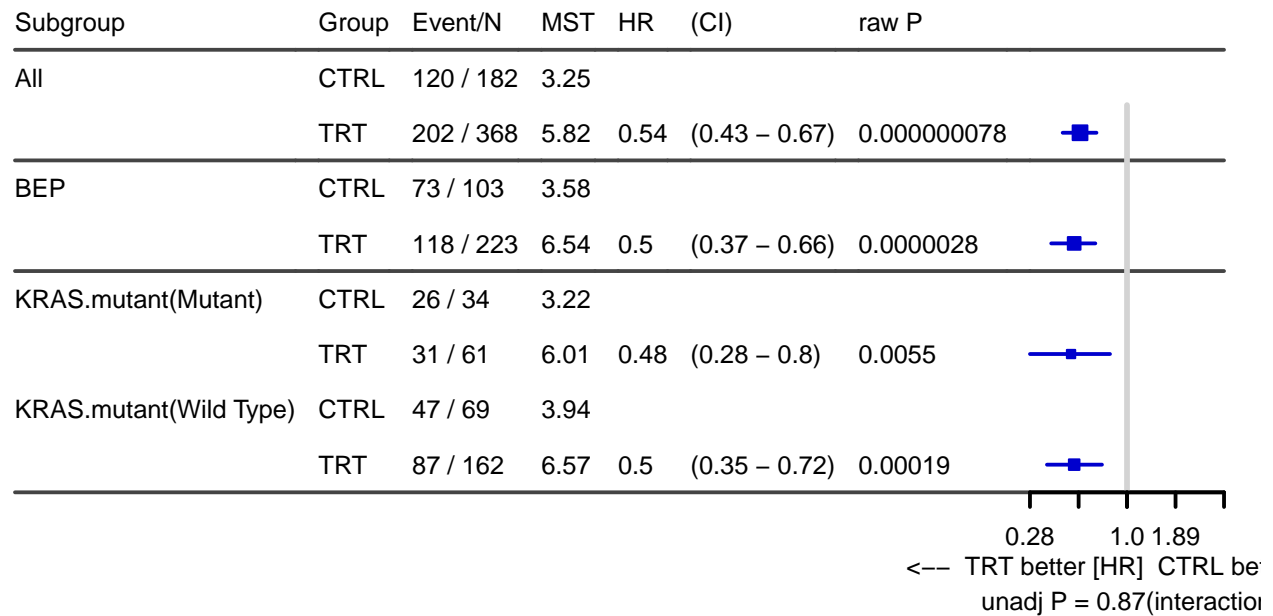
7.1 Survival outcome, 2-arm, categorical variable

by default BEP will be defined as patients non-NA biomarker measurement

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS","PFS.event"),
                        trt="Arm",
                        var="KRAS.mutant",
                        var.class="categorical")
```

Some NAs in var column, will define the non NA entries as BEP

Across-arm Effect of Biomarker **PFS, KRAS.mutant** **Unadjusted, unstratified analysis**



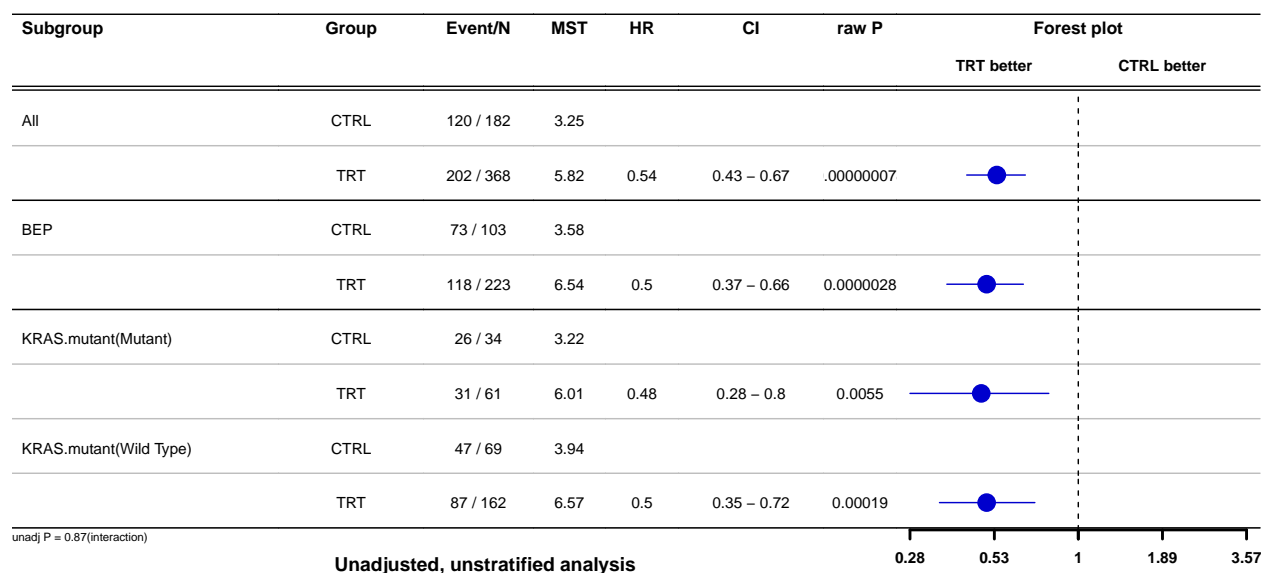
```
##
## code.v
## [1,] "Subgroup"      "Group" "Event/N" "MST" "HR"
## [2,] "All"           "CTRL"  "120 / 182" "3.25" ""
## [3,] ""              "TRT"   "202 / 368" "5.82" "0.54"
## [4,] "BEP"           "CTRL"  "73 / 103" "3.58" ""
## [5,] ""              "TRT"   "118 / 223" "6.54" "0.5"
## [6,] "KRAS.mutant(Mutant)" "CTRL"  "26 / 34" "3.22" ""
## [7,] ""              "TRT"   "31 / 61" "6.01" "0.48"
## [8,] "KRAS.mutant(Wild Type)" "CTRL"  "47 / 69" "3.94" ""
## [9,] ""              "TRT"   "87 / 162" "6.57" "0.5"
##
## [1,] "CI"           "raw P"
## [2,] ""             ""
## [3,] "0.43 - 0.67" "0.000000078"
## [4,] ""             ""
## [5,] "0.37 - 0.66" "0.0000028"
## [6,] ""             ""
## [7,] "0.28 - 0.8"  "0.0055"
## [8,] ""             ""
## [9,] "0.35 - 0.72" "0.00019"
```

7.2 Survival outcome, another format

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt="Arm",
                        var="KRAS.mutant",
                        var.class="categorical",
                        tabforest = TRUE)
```

Some NAs in var column, will define the non NA entries as BEP

Across-arm Effect of Biomarker PFS, KRAS.mutant



```
##
## code.v
## [1,] "Subgroup"      "Group" "Event/N" "MST" "HR"
## [2,] "All"          "CTRL"  "120 / 182" "3.25" ""
## [3,] ""             "TRT"   "202 / 368" "5.82" "0.54"
## [4,] "BEP"         "CTRL"  "73 / 103" "3.58" ""
## [5,] ""             "TRT"   "118 / 223" "6.54" "0.5"
## [6,] "KRAS.mutant(Mutant)" "CTRL"  "26 / 34" "3.22" ""
## [7,] ""             "TRT"   "31 / 61" "6.01" "0.48"
## [8,] "KRAS.mutant(Wild Type)" "CTRL"  "47 / 69" "3.94" ""
## [9,] ""             "TRT"   "87 / 162" "6.57" "0.5"
##
## [1,] "CI"          "raw P"
## [2,] ""            ""
## [3,] "0.43 - 0.67" "0.000000078"
## [4,] ""            ""
## [5,] "0.37 - 0.66" "0.0000028"
## [6,] ""            ""
## [7,] "0.28 - 0.8"  "0.0055"
```

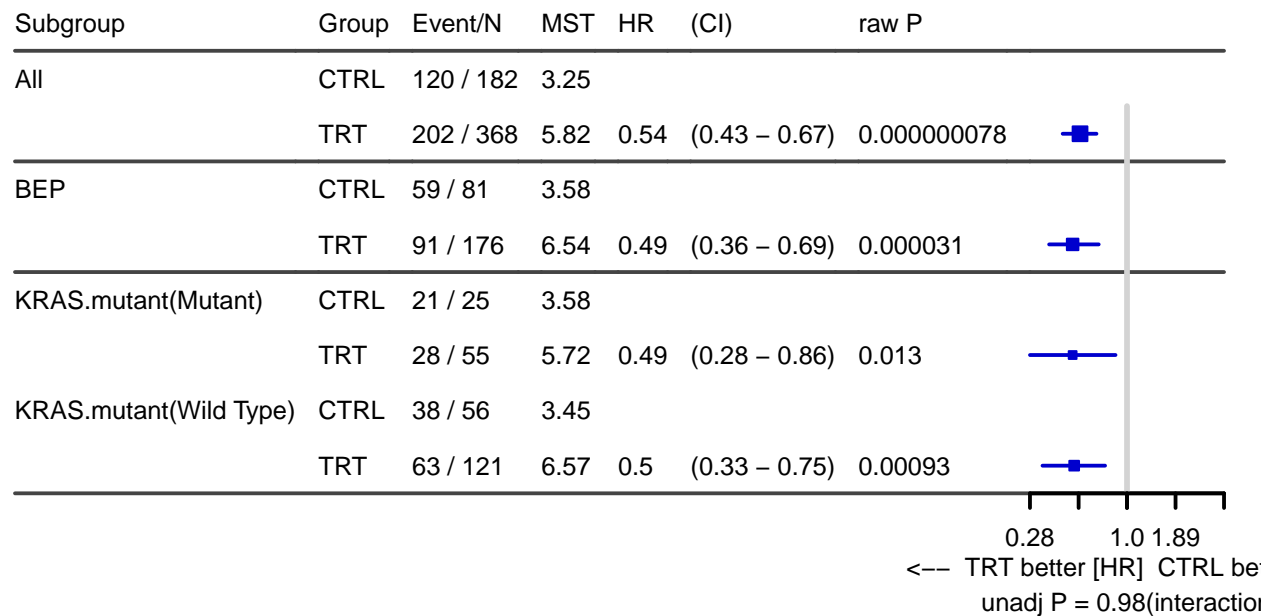
```
## [8,] "" ""
## [9,] "0.35 - 0.72" "0.00019"
```

7.3 Survival outcome, 2-arm, categorical variable, don't show ITT, BEP, re-name variable name in display

user can also define BEP column

```
PlotTabForestBiomarker(data=input,
  outcome.class="survival",
  outcome.var=c("PFS", "PFS.event"),
  trt="Arm",
  var="KRAS.mutant",
  var.class="categorical",
  bep = 'BEP',
  bep.indicator=1)
```

Across-arm Effect of Biomarker PFS, KRAS.mutant Unadjusted, unstratified analysis





```
## code.v
## [1,] "Subgroup" "Group" "Event/N" "MST" "HR"
## [2,] "All" "CTRL" "120 / 182" "3.25" ""
## [3,] "" "TRT" "202 / 368" "5.82" "0.54"
## [4,] "BEP" "CTRL" "59 / 81" "3.58" ""
## [5,] "" "TRT" "91 / 176" "6.54" "0.49"
## [6,] "KRAS.mutant(Mutant)" "CTRL" "21 / 25" "3.58" ""
## [7,] "" "TRT" "28 / 55" "5.72" "0.49"
```

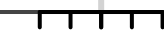
```
## [8,] "KRAS.mutant(Wild Type)" "CTRL" "38 / 56" "3.45" ""
## [9,] "" "TRT" "63 / 121" "6.57" "0.5"
##
## [1,] "CI" "raw P"
## [2,] "" ""
## [3,] "0.43 - 0.67" "0.000000078"
## [4,] "" ""
## [5,] "0.36 - 0.69" "0.000031"
## [6,] "" ""
## [7,] "0.28 - 0.86" "0.013"
## [8,] "" ""
## [9,] "0.33 - 0.75" "0.00093"
```

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS","PFS.event"),
                        trt="Arm",
                        var="KRAS.mutant",
                        var.class="categorical",
                        var.name="KRAS mut",
                        show.itt=FALSE,
                        show.bep=FALSE)
```

```
## Some NAs in var column, will define the non NA entries as BEP
```

Across-arm Effect of Biomarker PFS, KRAS mut Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P	
KRAS mut(Mutant)	CTRL	26 / 34	3.22				
	TRT	31 / 61	6.01	0.48	(0.28 - 0.8)	0.0055	
KRAS mut(Wild Type)	CTRL	47 / 69	3.94				
	TRT	87 / 162	6.57	0.5	(0.35 - 0.72)	0.00019	


 0.28 1.0 3.57
 <-- TRT better [HR] CTRL
 unadj P = 0.87(interac

```
##
## [1,] "Subgroup" "Group" "Event/N" "MST" "HR" "CI"
## [2,] "KRAS mut(Mutant)" "CTRL" "26 / 34" "3.22" "" ""
## [3,] "" "TRT" "31 / 61" "6.01" "0.48" "0.28 - 0.8"
## [4,] "KRAS mut(Wild Type)" "CTRL" "47 / 69" "3.94" "" ""
```

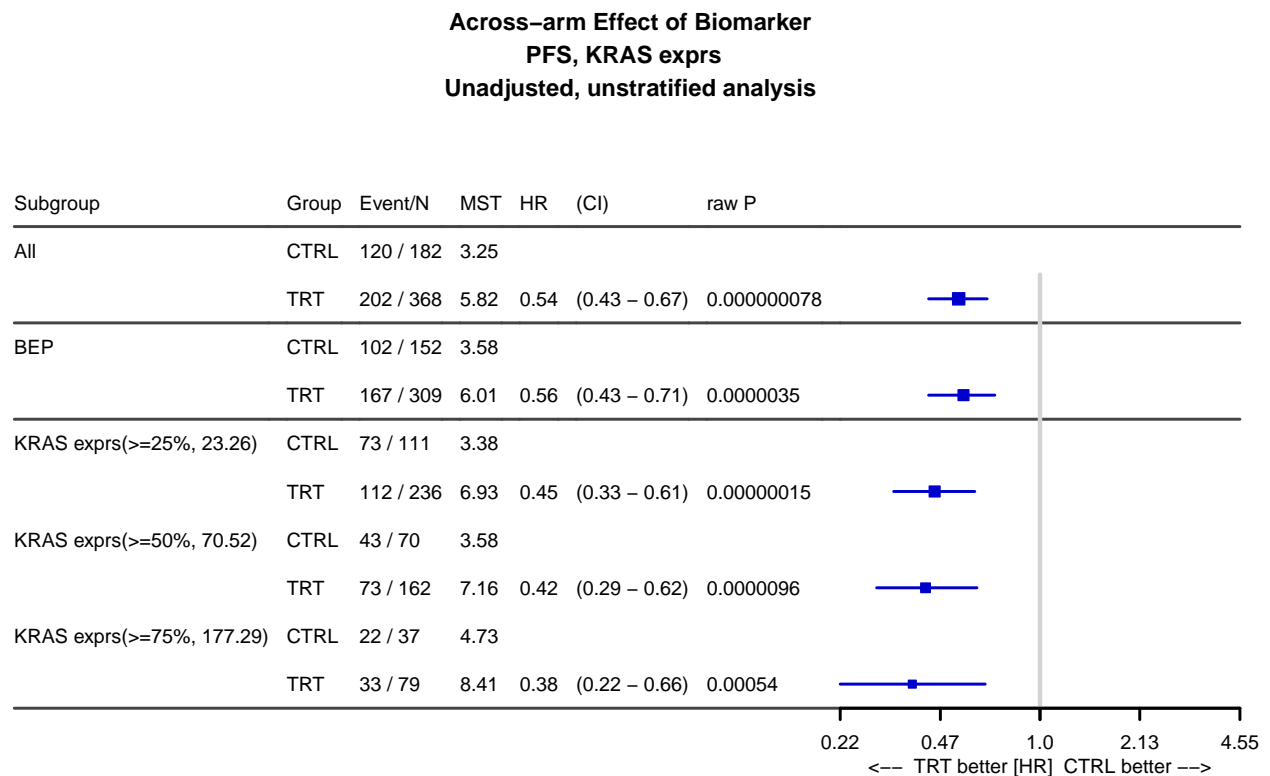


```
## [5,] "" "TRT" "87 / 162" "6.57" "0.5" "0.35 - 0.72"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.0055"
## [4,] ""
## [5,] "0.00019"
```

7.4 Survival outcome, 2-arm, continuous variable, greater than some percentage cutoffs

```
PlotTabForestBiomarker(data=input,
  outcome.class="survival",
  outcome.var=c("PFS","PFS.event"),
  trt="Arm",
  var="KRAS.exprs",
  var.class="numeric", var.name="KRAS exprs",
  percentile.cutoff=c(.25,.5,.75),
  # cols=c("black","black","darkgreen","darkgreen","darkgreen"),
  numerical.cutoff=NULL,
  greater=TRUE, less=FALSE,
  within.bin=FALSE,
  show.itt=TRUE, show.bep=TRUE)
```

Some NAs in var column, will define the non NA entries as BEP

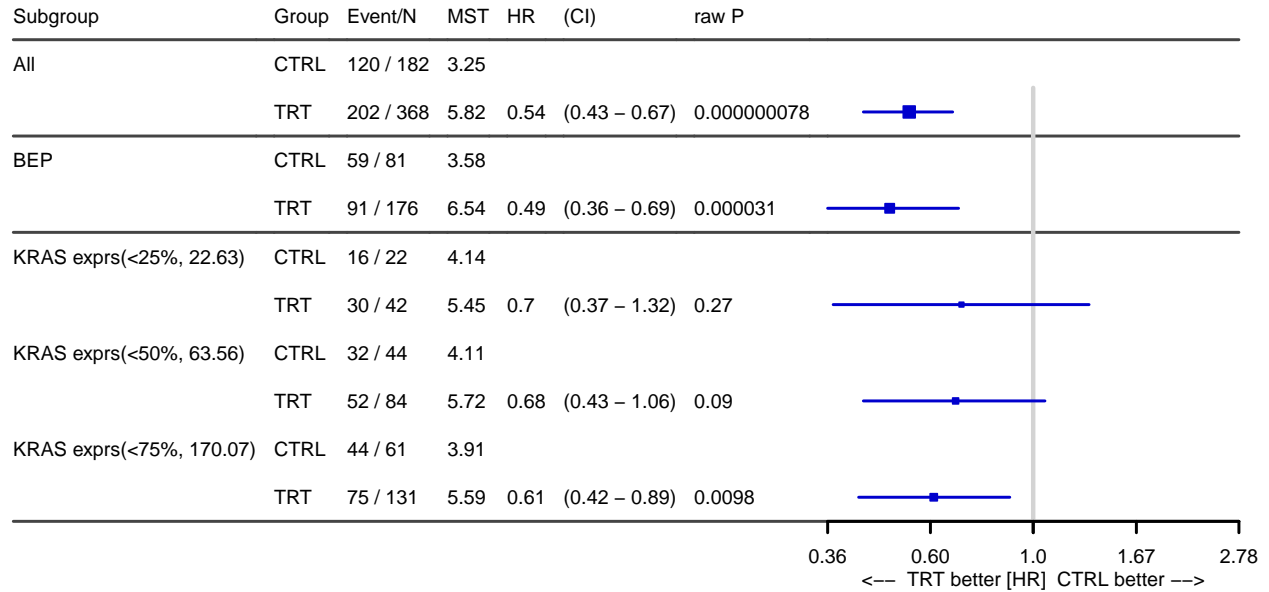


```
##                                     code.v
## [1,] "Subgroup"                    "Group" "Event/N"  "MST"  "HR"
## [2,] "All"                        "CTRL"  "120 / 182" "3.25" ""
## [3,] ""                           "TRT"   "202 / 368" "5.82" "0.54"
## [4,] "BEP"                        "CTRL"  "102 / 152" "3.58" ""
## [5,] ""                           "TRT"   "167 / 309" "6.01" "0.56"
## [6,] "KRAS exprs(>=25%, 23.26)"  "CTRL"  "73 / 111"  "3.38" ""
## [7,] ""                           "TRT"   "112 / 236" "6.93" "0.45"
## [8,] "KRAS exprs(>=50%, 70.52)"  "CTRL"  "43 / 70"   "3.58" ""
## [9,] ""                           "TRT"   "73 / 162"  "7.16" "0.42"
## [10,] "KRAS exprs(>=75%, 177.29)" "CTRL"  "22 / 37"   "4.73" ""
## [11,] ""                           "TRT"   "33 / 79"   "8.41" "0.38"
##
## [1,] "CI"                         "raw P"
## [2,] ""                           ""
## [3,] "0.43 - 0.67"                "0.000000078"
## [4,] ""                           ""
## [5,] "0.43 - 0.71"                "0.0000035"
## [6,] ""                           ""
## [7,] "0.33 - 0.61"                "0.0000015"
## [8,] ""                           ""
## [9,] "0.29 - 0.62"                "0.0000096"
## [10,] ""                          ""
## [11,] "0.22 - 0.66"               "0.00054"
```

7.5 Survival outcome, 2-arm, continuous variable, less than some percentage cutoffs

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=c(.25,.5,.75),
                        numerical.cutoff=NULL,
                        greater=FALSE, less=TRUE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE,
                        bep = 'BEP', bep.indicator=1)
```

Across-arm Effect of Biomarker
PFS, KRAS exprs
Unadjusted, unstratified analysis



```
##
## [1,] "Subgroup"
## [2,] "All"
## [3,] ""
## [4,] "BEP"
## [5,] ""
## [6,] "KRAS exprs(<25%, 22.63)"
## [7,] ""
## [8,] "KRAS exprs(<50%, 63.56)"
## [9,] ""
## [10,] "KRAS exprs(<75%, 170.07)"
## [11,] ""
##
## [1,] "CI"
## [2,] ""
## [3,] "0.43 - 0.67"
## [4,] ""
## [5,] "0.36 - 0.69"
## [6,] ""
## [7,] "0.37 - 1.32"
## [8,] ""
## [9,] "0.43 - 1.06"
## [10,] ""
## [11,] "0.42 - 0.89"

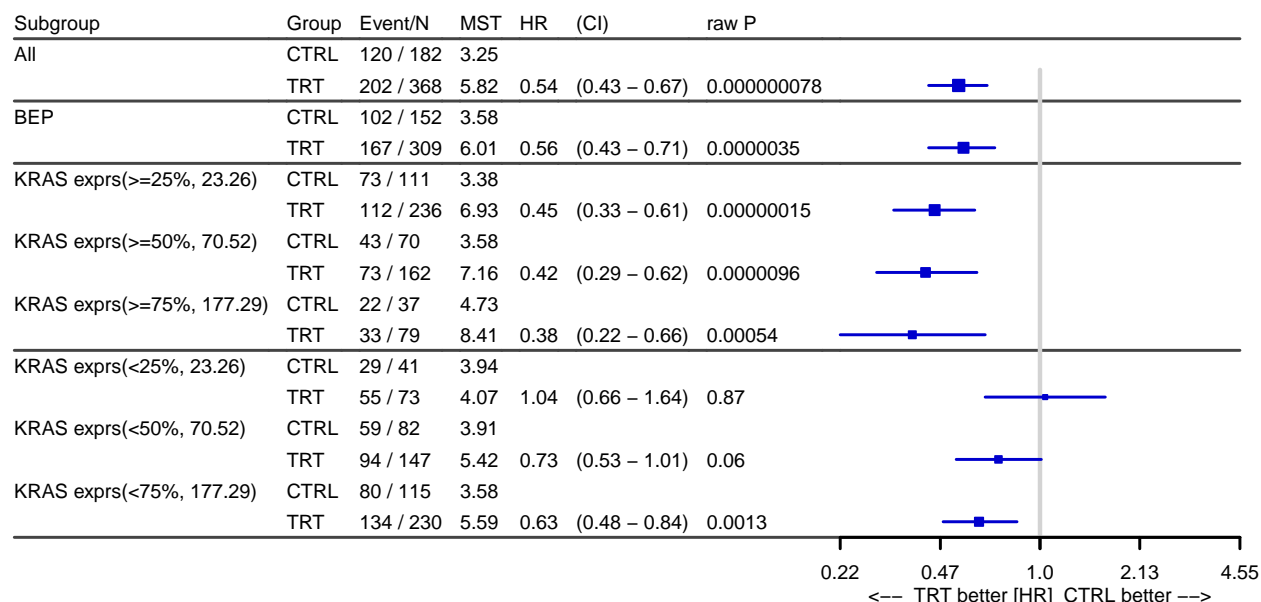
code.v
"Group" "Event/N" "MST" "HR"
"CTRL" "120 / 182" "3.25" ""
"TRT" "202 / 368" "5.82" "0.54"
"CTRL" "59 / 81" "3.58" ""
"TRT" "91 / 176" "6.54" "0.49"
"CTRL" "16 / 22" "4.14" ""
"TRT" "30 / 42" "5.45" "0.7"
"CTRL" "32 / 44" "4.11" ""
"TRT" "52 / 84" "5.72" "0.68"
"CTRL" "44 / 61" "3.91" ""
"TRT" "75 / 131" "5.59" "0.61"
"raw P"
""
"0.000000078"
""
"0.000031"
""
"0.27"
""
"0.09"
""
"0.0098"
```

7.6 Survival outcome, 2-arm, continuous variable, greater and less than some percentage cutoffs

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS","PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=c(.25,.5,.75),
                        numerical.cutoff=NULL,
                        greater=TRUE, less=TRUE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE)
```

Some NAs in var column, will define the non NA entries as BEP

Across-arm Effect of Biomarker PFS, KRAS exprs Unadjusted, unstratified analysis



```
##
## [1,] "Subgroup"      "Group" "Event/N"  "MST"  "HR"
## [2,] "All"           "CTRL"  "120 / 182" "3.25" ""
## [3,] ""              "TRT"   "202 / 368" "5.82" "0.54"
## [4,] "BEP"           "CTRL"  "102 / 152" "3.58" ""
## [5,] ""              "TRT"   "167 / 309" "6.01" "0.56"
## [6,] "KRAS exprs(>=25%, 23.26)" "CTRL"  "73 / 111"  "3.38" ""
## [7,] ""              "TRT"   "112 / 236" "6.93" "0.45"
## [8,] "KRAS exprs(>=50%, 70.52)" "CTRL"  "43 / 70"   "3.58" ""
```

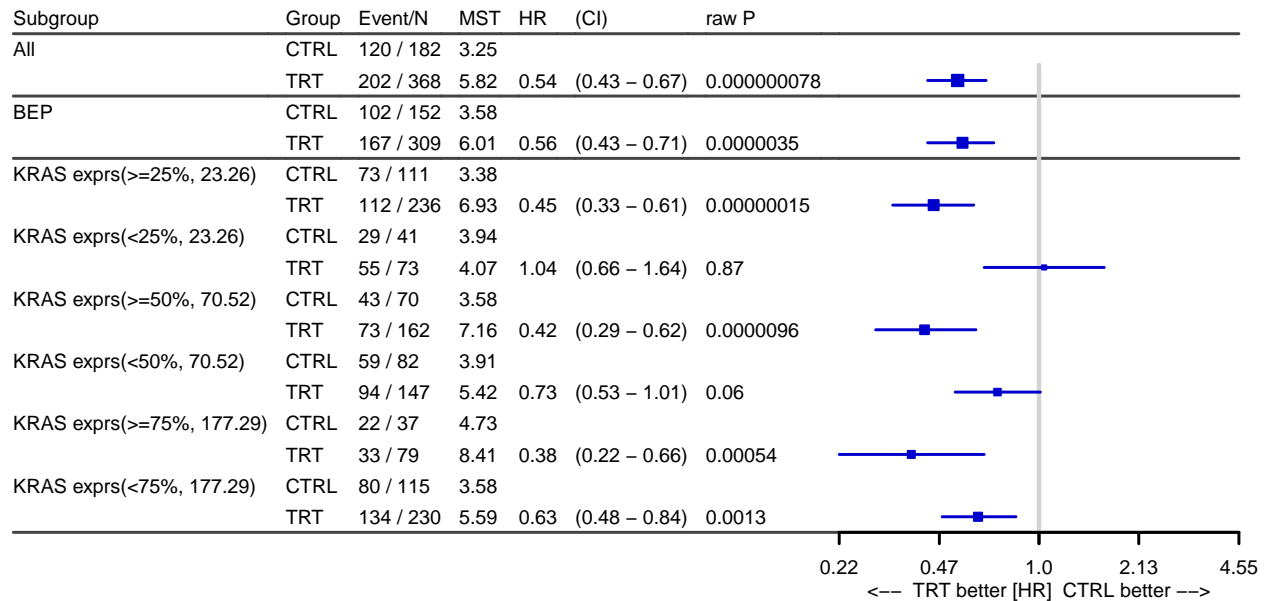
```
## [9,] "" "TRT" "73 / 162" "7.16" "0.42"
## [10,] "KRAS exprs(>=75%, 177.29)" "CTRL" "22 / 37" "4.73" ""
## [11,] "" "TRT" "33 / 79" "8.41" "0.38"
## [12,] "KRAS exprs(<25%, 23.26)" "CTRL" "29 / 41" "3.94" ""
## [13,] "" "TRT" "55 / 73" "4.07" "1.04"
## [14,] "KRAS exprs(<50%, 70.52)" "CTRL" "59 / 82" "3.91" ""
## [15,] "" "TRT" "94 / 147" "5.42" "0.73"
## [16,] "KRAS exprs(<75%, 177.29)" "CTRL" "80 / 115" "3.58" ""
## [17,] "" "TRT" "134 / 230" "5.59" "0.63"
##
## [1,] "CI" "raw P"
## [2,] "" ""
## [3,] "0.43 - 0.67" "0.000000078"
## [4,] "" ""
## [5,] "0.43 - 0.71" "0.0000035"
## [6,] "" ""
## [7,] "0.33 - 0.61" "0.00000015"
## [8,] "" ""
## [9,] "0.29 - 0.62" "0.0000096"
## [10,] "" ""
## [11,] "0.22 - 0.66" "0.00054"
## [12,] "" ""
## [13,] "0.66 - 1.64" "0.87"
## [14,] "" ""
## [15,] "0.53 - 1.01" "0.06"
## [16,] "" ""
## [17,] "0.48 - 0.84" "0.0013"
```

“Less” rows next to “Greater” rows:

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS","PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=c(.25,.5,.75),
                        numerical.cutoff=NULL,
                        greater=TRUE, less=TRUE, greater.by.less = TRUE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE)
```

```
## Some NAs in var column, will define the non NA entries as BEP
```

Across-arm Effect of Biomarker
PFS, KRAS exprs
Unadjusted, unstratified analysis



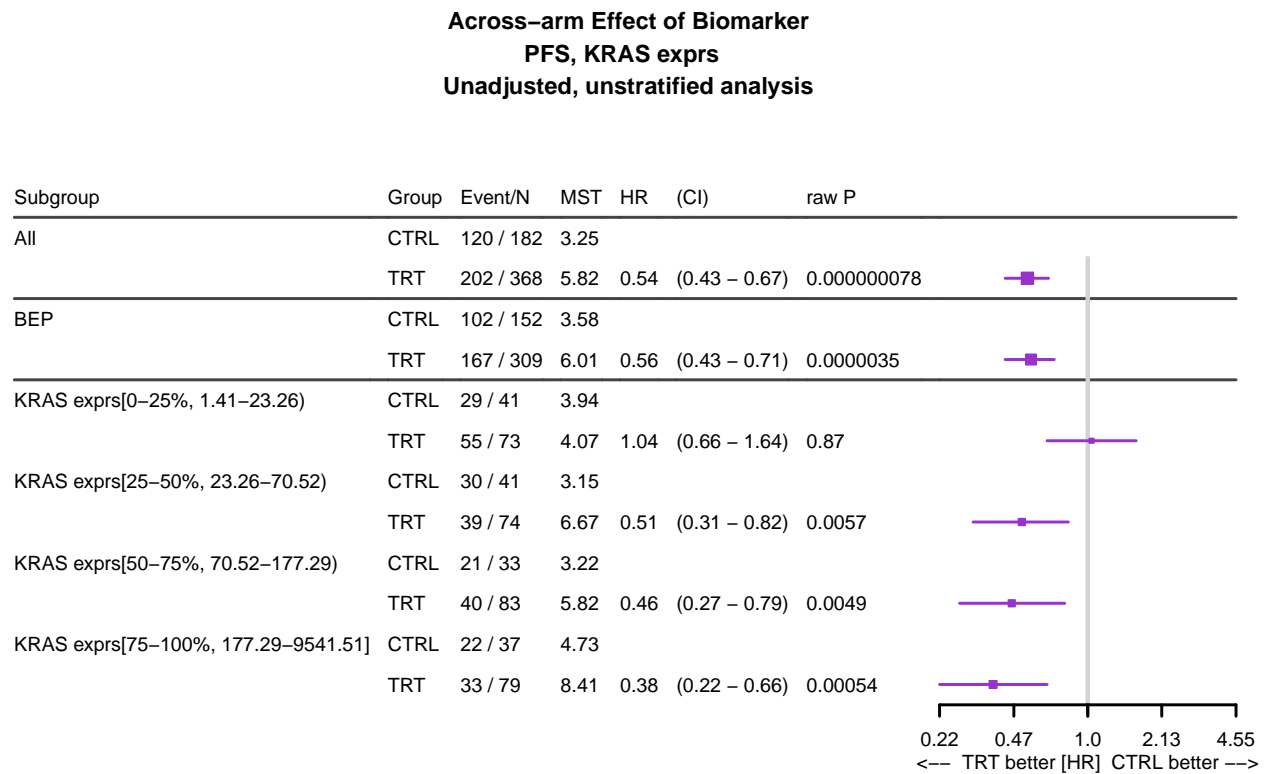
```
##
## [1,] "Subgroup"
## [2,] "All"
## [3,] ""
## [4,] "BEP"
## [5,] ""
## [6,] "KRAS exprs(>=25%, 23.26)"
## [7,] ""
## [8,] "KRAS exprs(<25%, 23.26)"
## [9,] ""
## [10,] "KRAS exprs(>=50%, 70.52)"
## [11,] ""
## [12,] "KRAS exprs(<50%, 70.52)"
## [13,] ""
## [14,] "KRAS exprs(>=75%, 177.29)"
## [15,] ""
## [16,] "KRAS exprs(<75%, 177.29)"
## [17,] ""
##
## [1,] "CI"          "raw P"
## [2,] ""           ""
## [3,] "0.43 - 0.67" "0.000000078"
## [4,] ""           ""
## [5,] "0.43 - 0.71" "0.0000035"
## [6,] ""           ""
## [7,] "0.33 - 0.61" "0.00000015"
## [8,] ""           ""
## [9,] "0.66 - 1.64" "0.87"
```

```
## [10,] "" ""
## [11,] "0.29 - 0.62" "0.0000096"
## [12,] "" ""
## [13,] "0.53 - 1.01" "0.06"
## [14,] "" ""
## [15,] "0.22 - 0.66" "0.00054"
## [16,] "" ""
## [17,] "0.48 - 0.84" "0.0013"
```

7.7 Survival outcome, 2-arm, continuous variable, within cutoff bin

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=c(.25,.5,.75),
                        numerical.cutoff=NULL,
                        greater=FALSE, less=FALSE,
                        within.bin=TRUE,
                        show.itt=TRUE, show.bep=TRUE)
```

Some NAs in var column, will define the non NA entries as BEP



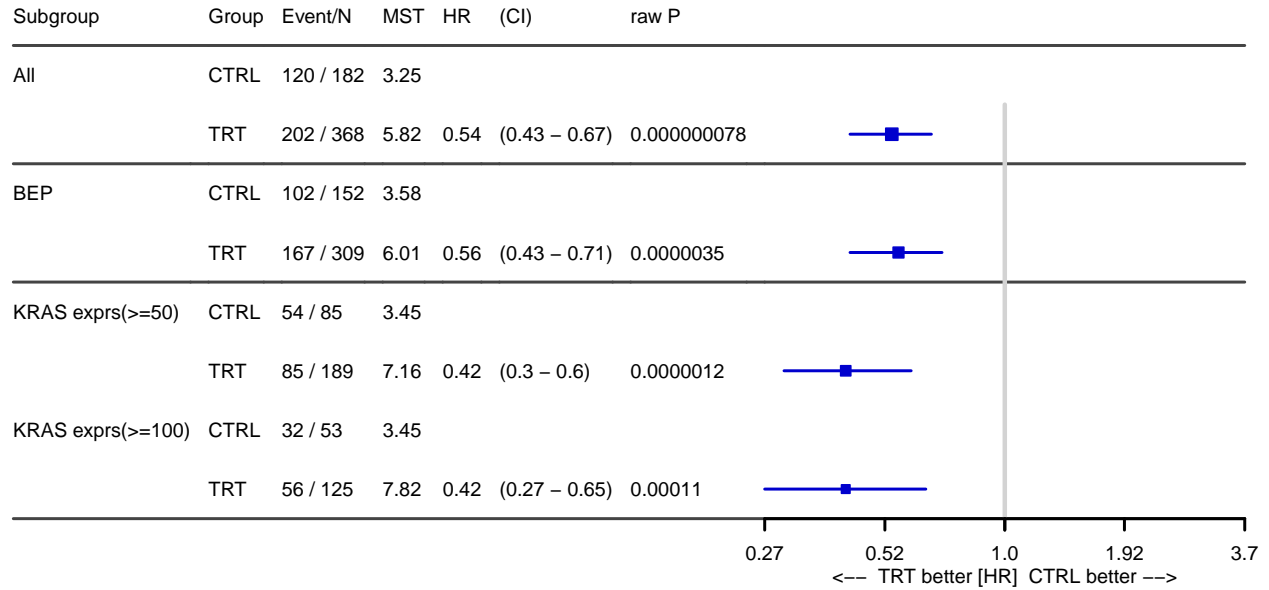
```
##                                     code.v
## [1,] "Subgroup"                    "Group" "Event/N"  "MST"
## [2,] "All"                        "CTRL"  "120 / 182" "3.25"
## [3,] ""                           "TRT"   "202 / 368" "5.82"
## [4,] "BEP"                        "CTRL"  "102 / 152" "3.58"
## [5,] ""                           "TRT"   "167 / 309" "6.01"
## [6,] "KRAS exprs[0-25%, 1.41-23.26)" "CTRL"  "29 / 41"  "3.94"
## [7,] ""                           "TRT"   "55 / 73"  "4.07"
## [8,] "KRAS exprs[25-50%, 23.26-70.52)" "CTRL"  "30 / 41"  "3.15"
## [9,] ""                           "TRT"   "39 / 74"  "6.67"
## [10,] "KRAS exprs[50-75%, 70.52-177.29)" "CTRL"  "21 / 33"  "3.22"
## [11,] ""                           "TRT"   "40 / 83"  "5.82"
## [12,] "KRAS exprs[75-100%, 177.29-9541.51]" "CTRL"  "22 / 37"  "4.73"
## [13,] ""                           "TRT"   "33 / 79"  "8.41"
##
## [1,] "HR"      "CI"      "raw P"
## [2,] ""        ""        ""
## [3,] "0.54"    "0.43 - 0.67" "0.000000078"
## [4,] ""        ""        ""
## [5,] "0.56"    "0.43 - 0.71" "0.0000035"
## [6,] ""        ""        ""
## [7,] "1.04"    "0.66 - 1.64" "0.87"
## [8,] ""        ""        ""
## [9,] "0.51"    "0.31 - 0.82" "0.0057"
## [10,] ""       ""        ""
## [11,] "0.46"   "0.27 - 0.79" "0.0049"
## [12,] ""       ""        ""
## [13,] "0.38"   "0.22 - 0.66" "0.00054"
```

7.8 Survival outcome, 2-arm, continuous variable, greater than some numerical cutoffs

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=NULL,
                        numerical.cutoff=c(50,100),
                        greater=TRUE, less=FALSE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE)
```

```
## Some NAs in var column, will define the non NA entries as BEP
```


Across-arm Effect of Biomarker
PFS, KRAS exprs
Unadjusted, unstratified analysis



```
##
## [1,] "Subgroup"      code.v
## [2,] "All"           "Group" "Event/N"  "MST"  "HR"  "CI"
## [3,] ""              "TRT"   "202 / 368" "5.82" "0.54" "0.43 - 0.67"
## [4,] "BEP"           "CTRL"  "102 / 152" "3.58" ""    ""
## [5,] ""              "TRT"   "167 / 309" "6.01" "0.56" "0.43 - 0.71"
## [6,] "KRAS exprs(>=50)" "CTRL"  "54 / 85"  "3.45" ""    ""
## [7,] ""              "TRT"   "85 / 189"  "7.16" "0.42" "0.3 - 0.6"
## [8,] "KRAS exprs(>=100)" "CTRL"  "32 / 53"  "3.45" ""    ""
## [9,] ""              "TRT"   "56 / 125"  "7.82" "0.42" "0.27 - 0.65"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.000000078"
## [4,] ""
## [5,] "0.0000035"
## [6,] ""
## [7,] "0.0000012"
## [8,] ""
## [9,] "0.00011"
```

7.9 Survival outcome, 2-arm, continuous variable, adjust for covariates

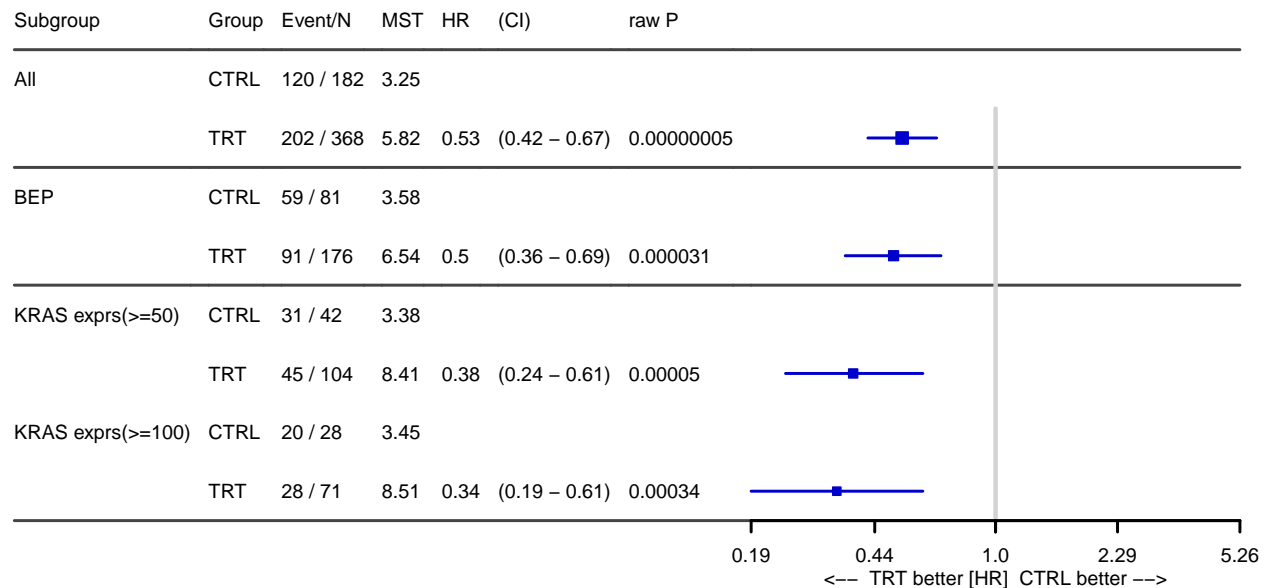
```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
```

```

trt="Arm",
var="KRAS.exprs",
var.class="numeric", var.name="KRAS exprs",
percentile.cutoff=NULL,
numerical.cutoff=c(50,100),
greater=TRUE, less=FALSE,
within.bin=FALSE,
show.itt=TRUE, show.bep=TRUE,
bep = 'BEP', bep.indicator=1, covariate="Age")

```

Across-arm Effect of Biomarker
PFS, KRAS exprs
Results adjusted by Age;



```

##
## [1,] "Subgroup"      "Group" "Event/N"  "MST"  "HR"  "CI"
## [2,] "All"           "CTRL"  "120 / 182"  "3.25" ""    ""
## [3,] ""              "TRT"   "202 / 368"  "5.82" "0.53" "0.42 - 0.67"
## [4,] "BEP"          "CTRL"  "59 / 81"   "3.58" ""    ""
## [5,] ""              "TRT"   "91 / 176"  "6.54" "0.5"  "0.36 - 0.69"
## [6,] "KRAS exprs(>=50)" "CTRL"  "31 / 42"   "3.38" ""    ""
## [7,] ""              "TRT"   "45 / 104"  "8.41" "0.38" "0.24 - 0.61"
## [8,] "KRAS exprs(>=100)" "CTRL"  "20 / 28"   "3.45" ""    ""
## [9,] ""              "TRT"   "28 / 71"   "8.51" "0.34" "0.19 - 0.61"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.00000005"
## [4,] ""
## [5,] "0.000031"
## [6,] ""

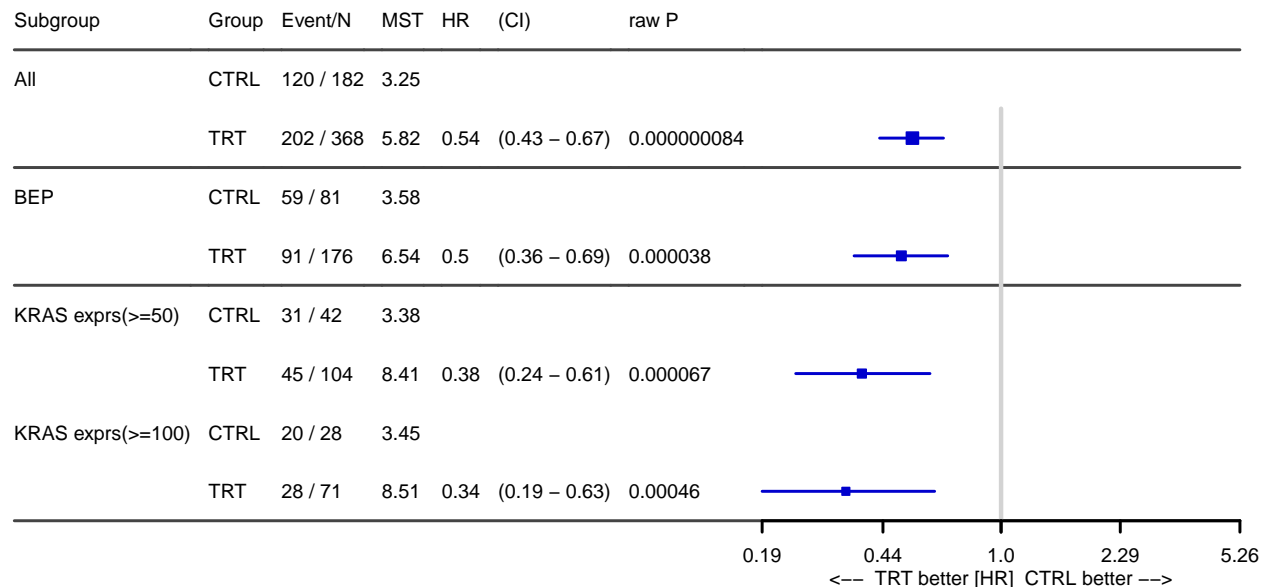
```

```
## [7,] "0.00005"
## [8,] ""
## [9,] "0.00034"
```

7.10 Survival outcome, 2-arm, continuous variable, stratification

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS","PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=NULL,
                        numerical.cutoff=c(50,100),
                        greater=TRUE, less=FALSE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE,
                        bep = 'BEP', bep.indicator=1, strata="Sex")
```

Across-arm Effect of Biomarker
PFS, KRAS exprs
;Results stratified by Sex



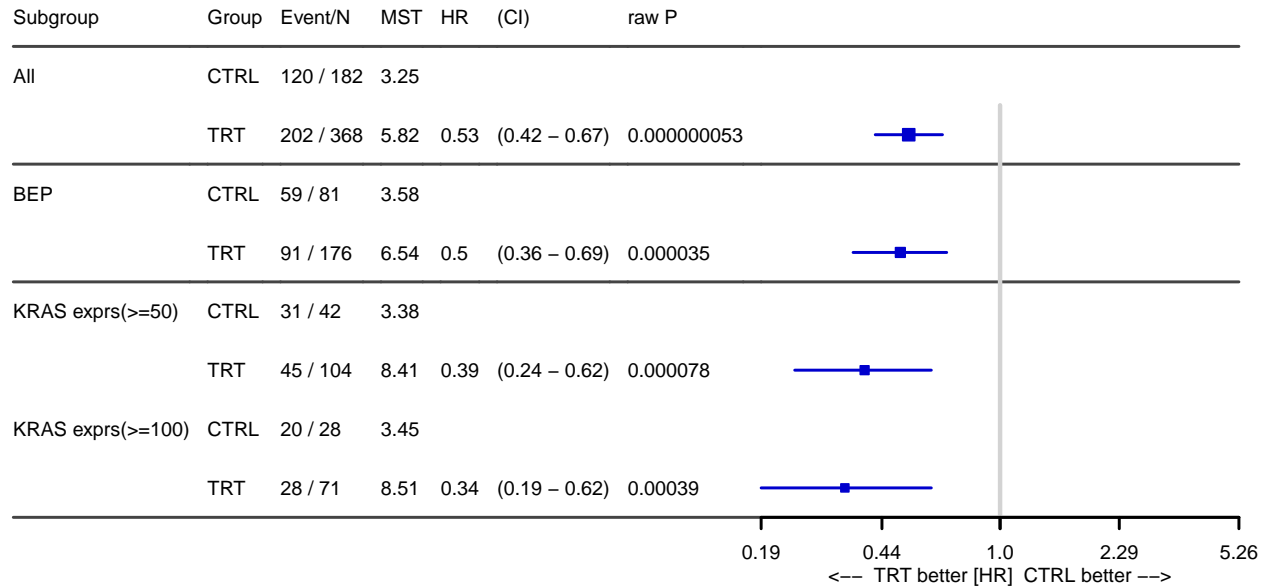
```
##
## [1,] "Subgroup"      "code.v"
## [2,] "All"           "Group" "Event/N" "MST" "HR" "CI"
## [3,] ""              "TRT"   "202 / 368" "5.82" "0.54" "0.43 - 0.67"
## [4,] "BEP"           "CTRL"  "59 / 81"   "3.58" ""   ""
## [5,] ""              "TRT"   "91 / 176"  "6.54" "0.5"  "0.36 - 0.69"
## [6,] "KRAS exprs(>=50)" "CTRL"  "31 / 42"   "3.38" ""   ""
```

```
## [7,] "" "TRT" "45 / 104" "8.41" "0.38" "0.24 - 0.61"
## [8,] "KRAS exprs(>=100)" "CTRL" "20 / 28" "3.45" "" ""
## [9,] "" "TRT" "28 / 71" "8.51" "0.34" "0.19 - 0.63"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.000000084"
## [4,] ""
## [5,] "0.000038"
## [6,] ""
## [7,] "0.000067"
## [8,] ""
## [9,] "0.00046"
```

7.11 Survival outcome, 2-arm, continuous variable, adjust for covariates and stratified by strata

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=NULL,
                        numerical.cutoff=c(50,100),
                        greater=TRUE, less=FALSE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE,
                        bep = 'BEP', bep.indicator=1, covariate="Age", strata="Sex")
```

Across-arm Effect of Biomarker
PFS, KRAS exprs
Results adjusted by Age;Results stratified by Sex



```
##
## code.v
## [1,] "Subgroup"      "Group" "Event/N" "MST" "HR" "CI"
## [2,] "All"           "CTRL"  "120 / 182" "3.25" "" ""
## [3,] ""              "TRT"   "202 / 368" "5.82" "0.53" "0.42 - 0.67"
## [4,] "BEP"          "CTRL"  "59 / 81" "3.58" "" ""
## [5,] ""              "TRT"   "91 / 176" "6.54" "0.5" "0.36 - 0.69"
## [6,] "KRAS exprs(>=50)" "CTRL"  "31 / 42" "3.38" "" ""
## [7,] ""              "TRT"   "45 / 104" "8.41" "0.39" "0.24 - 0.62"
## [8,] "KRAS exprs(>=100)" "CTRL"  "20 / 28" "3.45" "" ""
## [9,] ""              "TRT"   "28 / 71" "8.51" "0.34" "0.19 - 0.62"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.000000053"
## [4,] ""
## [5,] "0.000035"
## [6,] ""
## [7,] "0.000078"
## [8,] ""
## [9,] "0.00039"
```

7.12 Survival outcome, 1arm

within.bin, show.itt, show.bep will be ignored

```
PlotTabForestBiomarker(data=subset(input, Arm=="TRT"),
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt=NULL,
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=NULL,
                        numerical.cutoff=c(50,100),
                        greater=TRUE, less=FALSE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE, covariate="Age", strata="Sex")
```

```
## Some NAs in var column, will define the non NA entries as BEP
```

```
## only 1 arm; show.itt is set to FALSE
```

```
## only 1 arm; show.bep is set to FALSE
```

Within-arm Effect of Biomarker PFS, KRAS exprs Results adjusted by Age; Results stratified by Sex

Subgroup	Group	Event/N	MST	HR	(CI)	raw P	
KRAS exprs(>=50)	Less	82 / 120	5.39				
	Greater	85 / 189	7.16	0.54	(0.4 – 0.74)	0.000095	
KRAS exprs(>=100)	Less	111 / 184	5.59				
	Greater	56 / 125	7.82	0.57	(0.41 – 0.78)	0.00062	
							0.37 1.0 2.72 HR

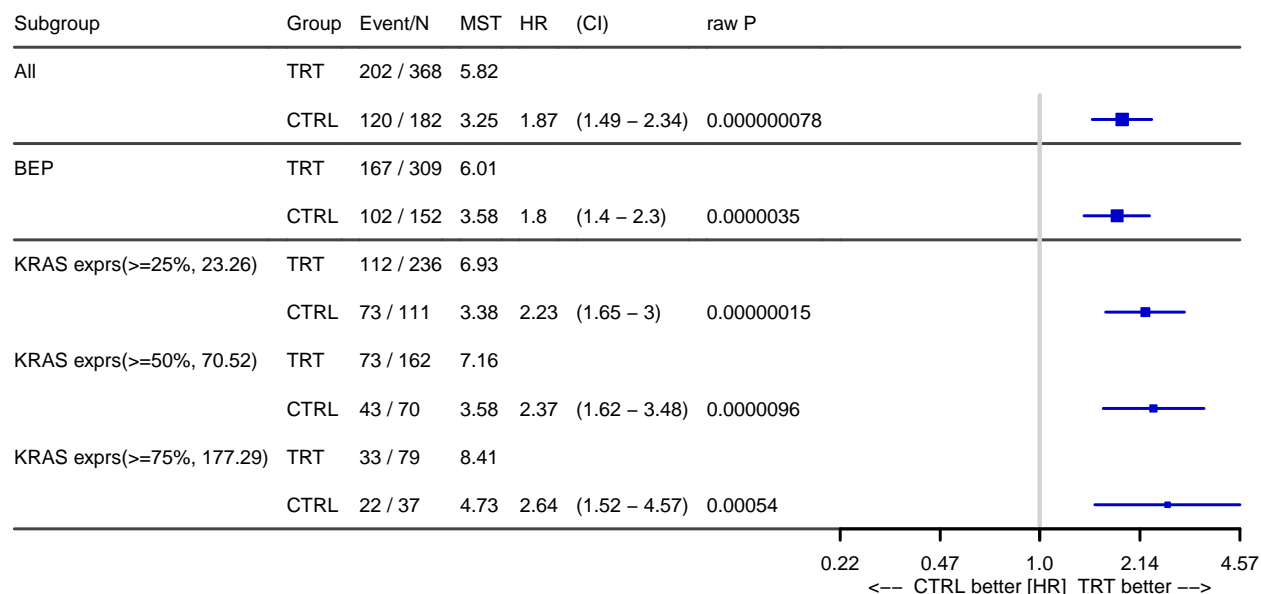
```
##
## [1,] "Subgroup"      code.v
## [2,] "KRAS exprs(>=50)" "Group"  "Event/N"  "MST"  "HR"  "CI"
## [3,] ""              "Greater" "85 / 189" "7.16" "0.54" "0.4 - 0.74"
## [4,] "KRAS exprs(>=100)" "Less"    "111 / 184" "5.59" ""    ""
## [5,] ""              "Greater" "56 / 125" "7.82" "0.57" "0.41 - 0.78"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.000095"
## [4,] ""
## [5,] "0.00062"
```

7.13 Survival outcome, 2arm, flip TRT/CTRL order (calculate ctrl over trt HR)

```
PlotTabForestBiomarker(data=input,
  outcome.class="survival",
  outcome.var=c("PFS","PFS.event"),
  trt="Arm",
  var="KRAS.exprs",
  var.class="numeric", var.name="KRAS exprs",
  percentile.cutoff=c(.25,.5,.75),
  numerical.cutoff=NULL,
  greater=TRUE, less=FALSE,
  within.bin=FALSE,
  show.itt=TRUE, show.bep=TRUE,
  covariate=NULL, #Sex
  strata=NULL, #Age
  placebo.code='TRT',
  active.code='CTRL')
```

Some NAs in var column, will define the non NA entries as BEP

Across-arm Effect of Biomarker PFS, KRAS exprs Unadjusted, unstratified analysis



```
##
## [1,] "Subgroup"      code.v
## [2,] "All"           "Group" "Event/N"  "MST"  "HR"
## [3,] ""              "TRT"   "202 / 368"  "5.82" ""
## [4,] "BEP"           "CTRL"  "120 / 182"  "3.25" "1.87"
## [5,] ""              "TRT"   "167 / 309"  "6.01" ""
```

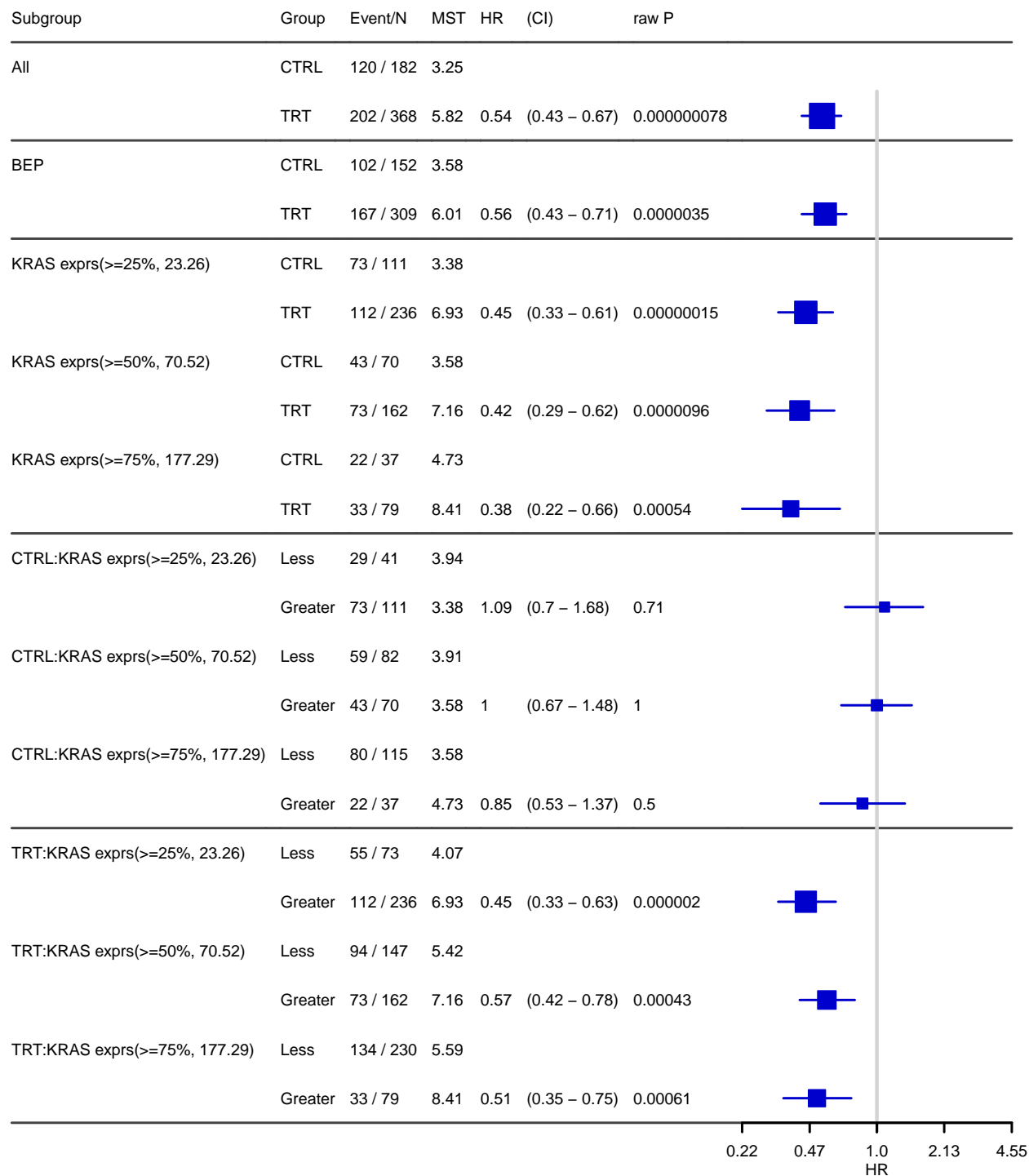
```
## [5,] "" "CTRL" "102 / 152" "3.58" "1.8"
## [6,] "KRAS exprs(>=25%, 23.26)" "TRT" "112 / 236" "6.93" ""
## [7,] "" "CTRL" "73 / 111" "3.38" "2.23"
## [8,] "KRAS exprs(>=50%, 70.52)" "TRT" "73 / 162" "7.16" ""
## [9,] "" "CTRL" "43 / 70" "3.58" "2.37"
## [10,] "KRAS exprs(>=75%, 177.29)" "TRT" "33 / 79" "8.41" ""
## [11,] "" "CTRL" "22 / 37" "4.73" "2.64"
##
## [1,] "CI" "raw P"
## [2,] "" ""
## [3,] "1.49 - 2.34" "0.000000078"
## [4,] "" ""
## [5,] "1.4 - 2.3" "0.0000035"
## [6,] "" ""
## [7,] "1.65 - 3" "0.00000015"
## [8,] "" ""
## [9,] "1.62 - 3.48" "0.0000096"
## [10,] "" ""
## [11,] "1.52 - 4.57" "0.00054"
```

7.14 Survival outcome, 2-arm, continuous variable, greater than some percentage cutoffs, show across-arm and within-arm results in the same plot

```
PlotTabForestBiomarker(data=input,
                        outcome.class="survival",
                        outcome.var=c("PFS", "PFS.event"),
                        trt="Arm",
                        var="KRAS.exprs",
                        var.class="numeric", var.name="KRAS exprs",
                        percentile.cutoff=c(.25,.5,.75),
                        numerical.cutoff=NULL,
                        greater=TRUE, less=FALSE,
                        within.bin=FALSE,
                        show.itt=TRUE, show.bep=TRUE,
                        across.and.within = TRUE)
```

```
## Some NAs in var column, will define the non NA entries as BEP
```


Across-arm and Within-arm Effect of Biomarker
PFS, KRAS exprs
Unadjusted, unstratified analysis



```
##
## [1,] "Subgroup"
## code.v
## "Group" "Event/N" "MST" "HR"
```

```

## [2,] "All" "CTRL" "120 / 182" "3.25" ""
## [3,] "" "TRT" "202 / 368" "5.82" "0.54"
## [4,] "BEP" "CTRL" "102 / 152" "3.58" ""
## [5,] "" "TRT" "167 / 309" "6.01" "0.56"
## [6,] "KRAS exprs(>=25%, 23.26)" "CTRL" "73 / 111" "3.38" ""
## [7,] "" "TRT" "112 / 236" "6.93" "0.45"
## [8,] "KRAS exprs(>=50%, 70.52)" "CTRL" "43 / 70" "3.58" ""
## [9,] "" "TRT" "73 / 162" "7.16" "0.42"
## [10,] "KRAS exprs(>=75%, 177.29)" "CTRL" "22 / 37" "4.73" ""
## [11,] "" "TRT" "33 / 79" "8.41" "0.38"
## [12,] "CTRL:KRAS exprs(>=25%, 23.26)" "Less" "29 / 41" "3.94" ""
## [13,] "" "Greater" "73 / 111" "3.38" "1.09"
## [14,] "CTRL:KRAS exprs(>=50%, 70.52)" "Less" "59 / 82" "3.91" ""
## [15,] "" "Greater" "43 / 70" "3.58" "1"
## [16,] "CTRL:KRAS exprs(>=75%, 177.29)" "Less" "80 / 115" "3.58" ""
## [17,] "" "Greater" "22 / 37" "4.73" "0.85"
## [18,] "TRT:KRAS exprs(>=25%, 23.26)" "Less" "55 / 73" "4.07" ""
## [19,] "" "Greater" "112 / 236" "6.93" "0.45"
## [20,] "TRT:KRAS exprs(>=50%, 70.52)" "Less" "94 / 147" "5.42" ""
## [21,] "" "Greater" "73 / 162" "7.16" "0.57"
## [22,] "TRT:KRAS exprs(>=75%, 177.29)" "Less" "134 / 230" "5.59" ""
## [23,] "" "Greater" "33 / 79" "8.41" "0.51"
##
## [1,] "CI" "raw P"
## [2,] "" ""
## [3,] "0.43 - 0.67" "0.000000078"
## [4,] "" ""
## [5,] "0.43 - 0.71" "0.0000035"
## [6,] "" ""
## [7,] "0.33 - 0.61" "0.00000015"
## [8,] "" ""
## [9,] "0.29 - 0.62" "0.0000096"
## [10,] "" ""
## [11,] "0.22 - 0.66" "0.00054"
## [12,] "" ""
## [13,] "0.7 - 1.68" "0.71"
## [14,] "" ""
## [15,] "0.67 - 1.48" "1"
## [16,] "" ""
## [17,] "0.53 - 1.37" "0.5"
## [18,] "" ""
## [19,] "0.33 - 0.63" "0.000002"
## [20,] "" ""
## [21,] "0.42 - 0.78" "0.00043"
## [22,] "" ""
## [23,] "0.35 - 0.75" "0.00061"

```

7.15 Response outcome, 2-arm, categorical variable

by default BEP will be defined as patients non-NA biomarker measurement

```

PlotTabForestBiomarker(data=input,
                        outcome.class="binary",

```

```





outcome.var=c("Response"),
rsp.cat = TRUE,
rsp.response = c("CR","PR"),
rsp.nonresponse = c("SD", "PD","NON CR/PD","NE",NA),
trt="Arm",
var="KRAS.mutant",
var.class="categorical")


```

Covariate adjustment and stratification are not supported for binary outcome

Some NAs in var column, will define the non NA entries as BEP

Across-arm Effect of Biomarker **Response, KRAS.mutant** **Unadjusted, unstratified analysis**

Subgroup	Group	nRsp/N	Rsp Rate	deltaRR	(CI)	raw P	
All	CTRL	14 / 182	0.08				
	TRT	96 / 368	0.26	0.18	(0.12 – 0.25)	0.0000007	
BEP	CTRL	11 / 103	0.11				
	TRT	54 / 223	0.24	0.14	(0.05 – 0.22)	0.007	
KRAS.mutant(Mutant)	CTRL	5 / 34	0.15				
	TRT	18 / 61	0.3	0.15	(-0.04 – 0.34)	0.17	
KRAS.mutant(Wild Type)	CTRL	6 / 69	0.09				
	TRT	36 / 162	0.22	0.14	(0.03 – 0.24)	0.024	


 -0.34 0 0.34
 <-- CTRL better [deltaRR] TF
 * Unadj P = 0.77 (intera

```

##
##      code.v
## [1,] "Subgroup"      "Group" "nRsp/N"  "Rsp Rate" "deltaRR"
## [2,] "All"           "CTRL"  "14 / 182" "0.08"     ""
## [3,] ""              "TRT"   "96 / 368" "0.26"     "0.18"
## [4,] "BEP"           "CTRL"  "11 / 103" "0.11"     ""
## [5,] ""              "TRT"   "54 / 223" "0.24"     "0.14"
## [6,] "KRAS.mutant(Mutant)" "CTRL"  "5 / 34"  "0.15"     ""
## [7,] ""              "TRT"   "18 / 61"  "0.3"      "0.15"
## [8,] "KRAS.mutant(Wild Type)" "CTRL"  "6 / 69"  "0.09"     ""
## [9,] ""              "TRT"   "36 / 162" "0.22"     "0.14"
##
## [1,] "CI"           "raw P"
## [2,] ""             ""

```

```
## [3,] "0.12 - 0.25" "0.0000007"
## [4,] "" ""
## [5,] "0.05 - 0.22" "0.007"
## [6,] "" ""
## [7,] "-0.04 - 0.34" "0.17"
## [8,] "" ""
## [9,] "0.03 - 0.24" "0.024"
```

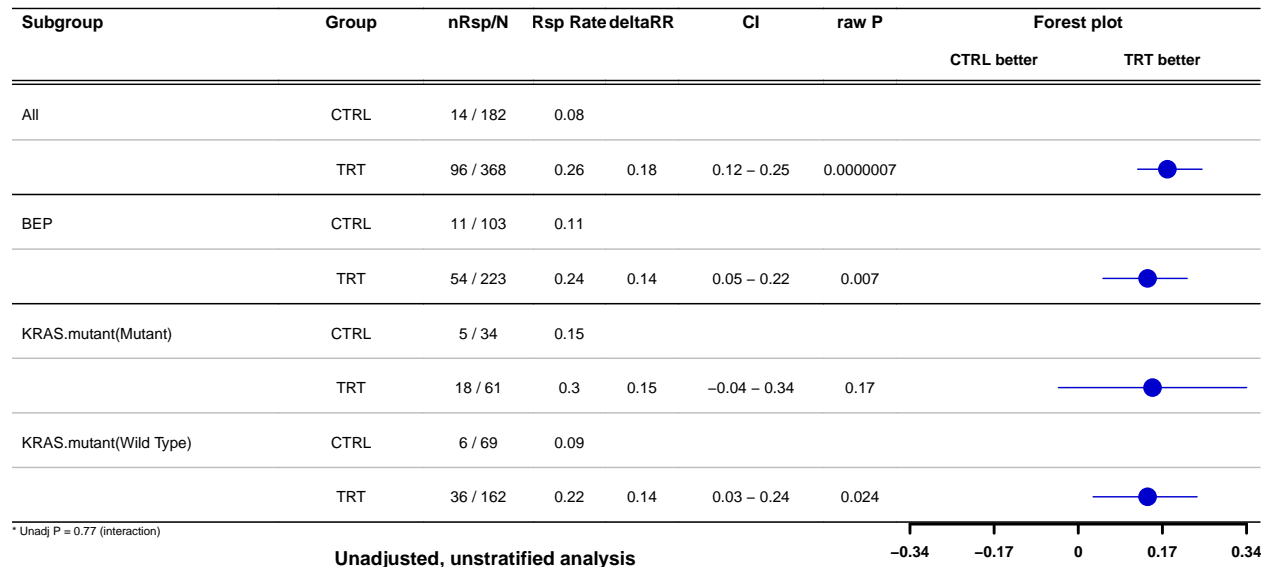
7.16 Response outcome, another format

```
PlotTabForestBiomarker(data=input,
                        outcome.class="binary",
                        outcome.var=c("Response"),
                        rsp.cat = TRUE,
                        rsp.response = c("CR","PR"),
                        rsp.nonresponse = c("SD", "PD","NON CR/PD","NE",NA),
                        trt="Arm",
                        var="KRAS.mutant",
                        var.class="categorical",
                        tabforest = TRUE)
```

```
## Covariate adjustment and stratification are not supported for binary outcome
```

```
## Some NAs in var column, will define the non NA entries as BEP
```

Across-arm Effect of Biomarker Response, KRAS.mutant



```
## code.v
## [1,] "Subgroup" "Group" "nRsp/N" "Rsp Rate" "deltaRR"
## [2,] "All" "CTRL" "14 / 182" "0.08" ""
## [3,] "" "TRT" "96 / 368" "0.26" "0.18"
```

```
## [4,] "BEP" "CTRL" "11 / 103" "0.11" ""
## [5,] "" "TRT" "54 / 223" "0.24" "0.14"
## [6,] "KRAS.mutant(Mutant)" "CTRL" "5 / 34" "0.15" ""
## [7,] "" "TRT" "18 / 61" "0.3" "0.15"
## [8,] "KRAS.mutant(Wild Type)" "CTRL" "6 / 69" "0.09" ""
## [9,] "" "TRT" "36 / 162" "0.22" "0.14"
##
## [1,] "CI" "raw P"
## [2,] "" ""
## [3,] "0.12 - 0.25" "0.0000007"
## [4,] "" ""
## [5,] "0.05 - 0.22" "0.007"
## [6,] "" ""
## [7,] "-0.04 - 0.34" "0.17"
## [8,] "" ""
## [9,] "0.03 - 0.24" "0.024"
```

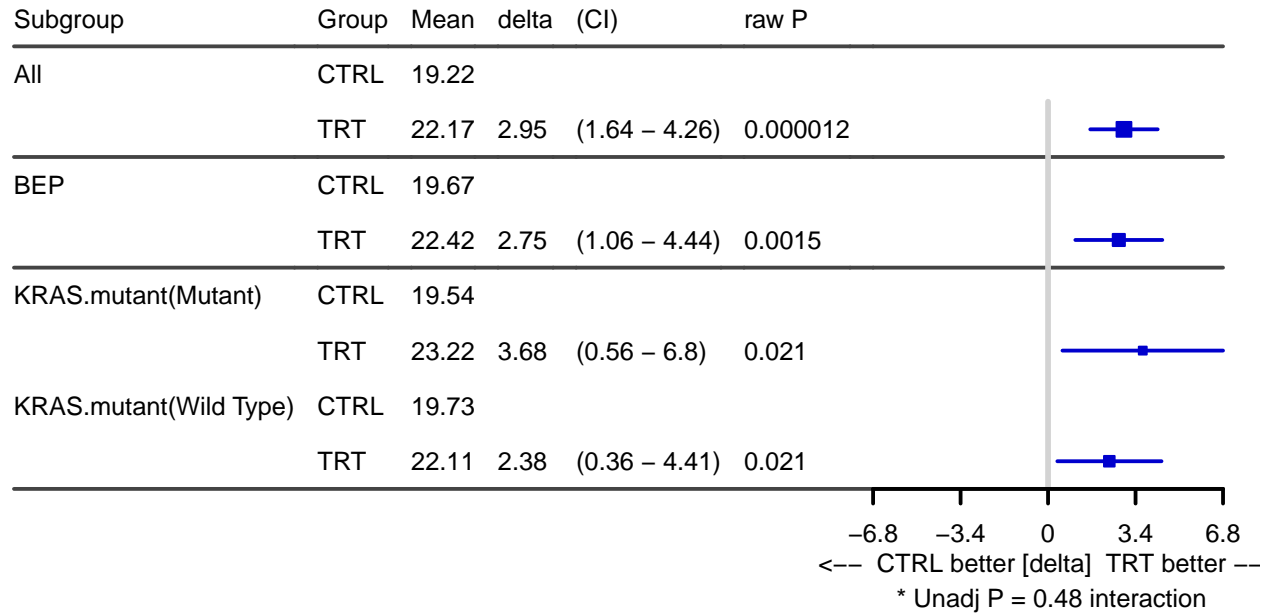
7.17 Continuous outcome, 2-arm, categorical variable

```
PlotTabForestBiomarker(data=input,
                        outcome.class="continuous",
                        outcome.var=c("Lab_ontrt"),
                        trt="Arm",
                        var="KRAS.mutant",
                        var.class="categorical")
```

```
## Stratification is not supported for continuous outcome
```

```
## Some NAs in var column, will define the non NA entries as BEP
```

Across-arm Effect of Biomarker
Lab_ontrt, KRAS.mutant
Unadjusted, unstratified analysis



```
##                               code.v
## [1,] "Subgroup"              "Group" "Mean" "delta" "CI"
## [2,] "All"                   "CTRL"  "19.22" ""      ""
## [3,] ""                      "TRT"   "22.17" "2.95" "1.64 - 4.26"
## [4,] "BEP"                   "CTRL"  "19.67" ""      ""
## [5,] ""                      "TRT"   "22.42" "2.75" "1.06 - 4.44"
## [6,] "KRAS.mutant(Mutant)"   "CTRL"  "19.54" ""      ""
## [7,] ""                      "TRT"   "23.22" "3.68" "0.56 - 6.8"
## [8,] "KRAS.mutant(Wild Type)" "CTRL"  "19.73" ""      ""
## [9,] ""                      "TRT"   "22.11" "2.38" "0.36 - 4.41"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.000012"
## [4,] ""
## [5,] "0.0015"
## [6,] ""
## [7,] "0.021"
## [8,] ""
## [9,] "0.021"
```

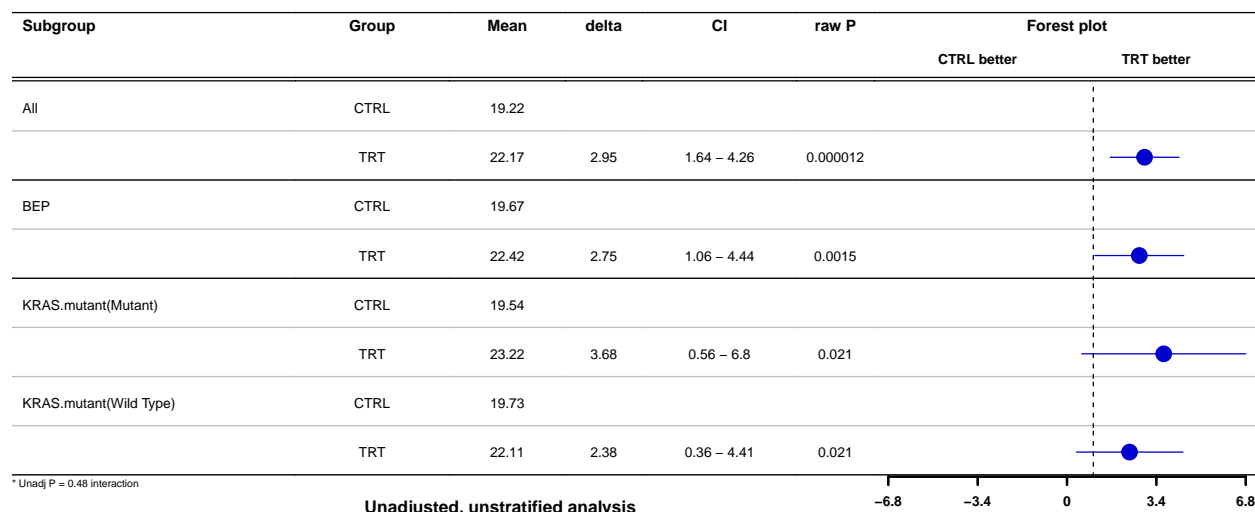
```
PlotTabForestBiomarker(data=input,
                        outcome.class="continuous",
                        outcome.var=c("Lab_ontrt"),
                        trt="Arm",
                        var="KRAS.mutant",
```

```
var.class="categorical",tabforest=T)
```

```
## Stratification is not supported for continuous outcome
```

```
## Some NAs in var column, will define the non NA entries as BEP
```

Across-arm Effect of Biomarker Lab_ontrt, KRAS.mutant



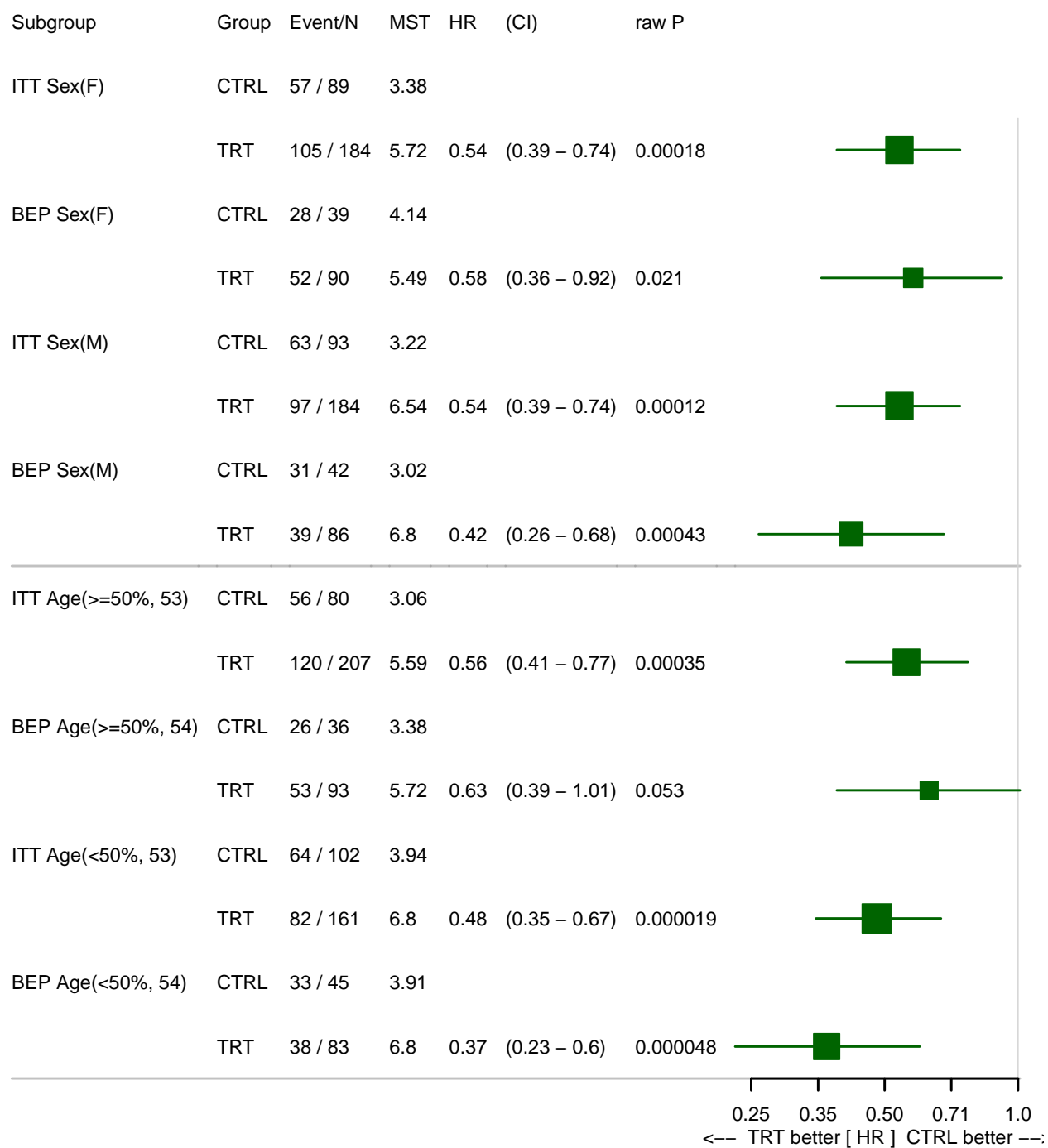
```
##
## [1,] "Subgroup"      code.v
## [2,] "All"          "Group" "Mean" "delta" "CI"
## [3,] ""             "CTRL"  "19.22" ""      ""
## [4,] "BEP"          "TRT"   "22.17" "2.95" "1.64 - 4.26"
## [5,] ""             "CTRL"  "19.67" ""      ""
## [6,] "KRAS.mutant(Mutant)" "TRT"   "22.42" "2.75" "1.06 - 4.44"
## [7,] ""             "CTRL"  "19.54" ""      ""
## [8,] "KRAS.mutant(Wild Type)" "TRT"   "23.22" "3.68" "0.56 - 6.8"
## [9,] ""             "CTRL"  "19.73" ""      ""
## [10,] ""            "TRT"   "22.11" "2.38" "0.36 - 4.41"
##
## [1,] "raw P"
## [2,] ""
## [3,] "0.000012"
## [4,] ""
## [5,] "0.0015"
## [6,] ""
## [7,] "0.021"
## [8,] ""
## [9,] "0.021"
```

8 PlotTabForestMulti(): Forest plots to compare multiple variates' effect in ITT vs BEP, or compare multiple variates' effect in subpopulations

8.1 2-arm, compare BEP vs ITT

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS", "PFS.event"),
                    trt="Arm",
                    var=c("Sex", "Age"),
                    bep="BEP", bep.indicator=1,
                    compare.bep.itt=TRUE
                    )
```


**Across arm, Compare BEP vs. All
PFS
Unadjusted, unstratified analysis**



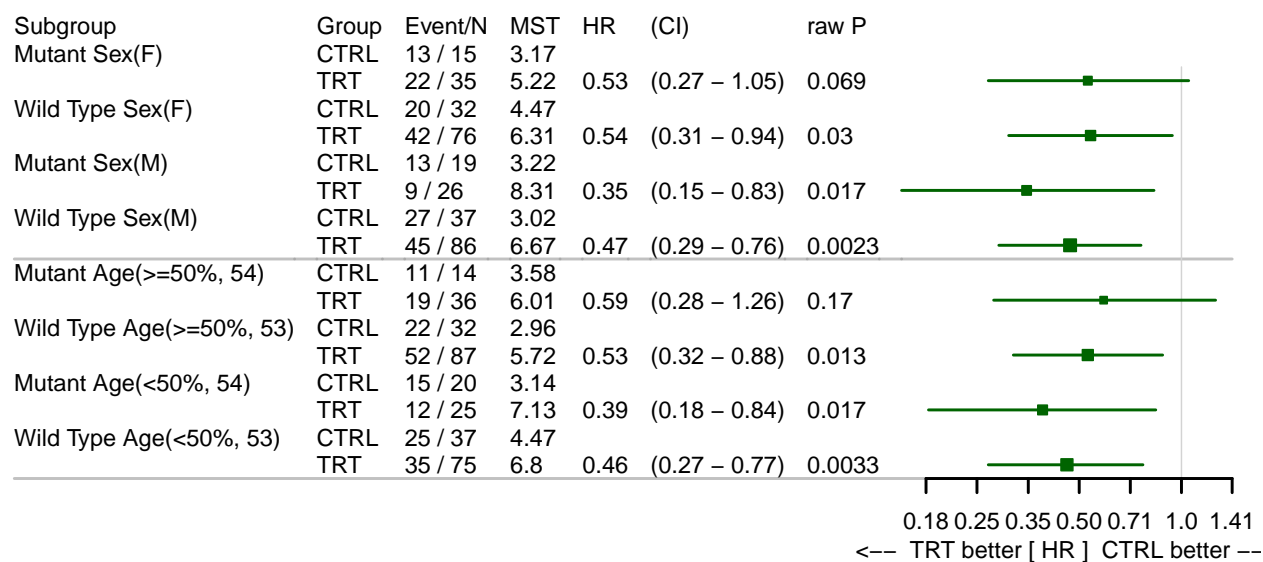
8.2 2-arm, compare subgroups defined by biomarker

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS", "PFS.event"),
                    trt="Arm",
                    var=c("Sex", "Age"),
                    bep="BEP", bep.indicator=1, compare.bep.itt=FALSE,
                    compare.subgroup=TRUE, subgroup="KRAS.mutant"
)
```

Across arm, Compare KRAS.mutant subgroup

PFS

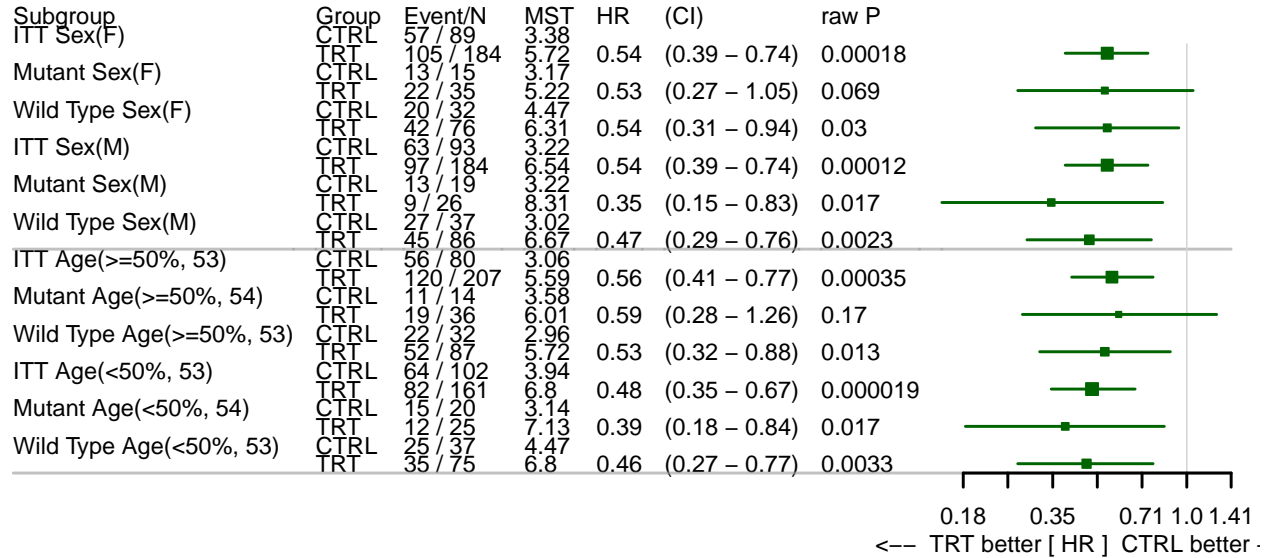
Unadjusted, unstratified analysis



8.3 2-arm, compare subgroups defined by biomarker, also show ITT

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS", "PFS.event"),
                    trt="Arm",
                    var=c("Sex", "Age"),
                    bep="BEP", bep.indicator=1, compare.bep.itt=FALSE,
                    compare.subgroup=TRUE, subgroup="KRAS.mutant", show.itt=TRUE
)
```

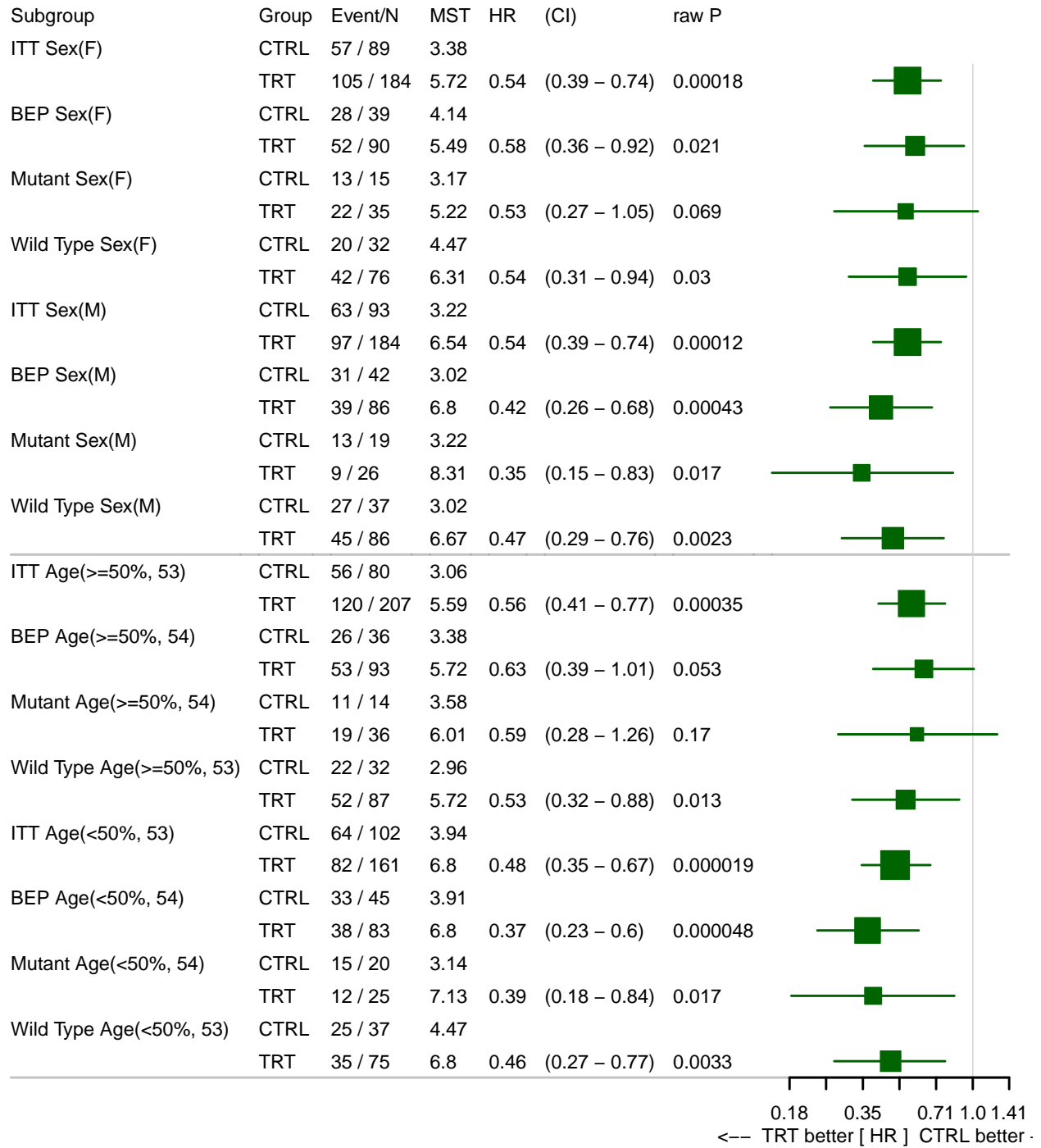
Across arm, Compare KRAS.mutant subgroup
PFS
Unadjusted, unstratified analysis



8.4 2-arm, compare subgroups defined by biomarker, also show BEP

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS", "PFS.event"),
                    trt="Arm",
                    var=c("Sex", "Age"),
                    bep="BEP", bep.indicator=1, compare.bep.itt=FALSE,
                    compare.subgroup=TRUE, subgroup="KRAS.mutant", show.itt=TRUE, show.bep=TRUE
                    )
```

Across arm, Compare KRAS.mutant subgroup
PFS
Unadjusted, unstratified analysis

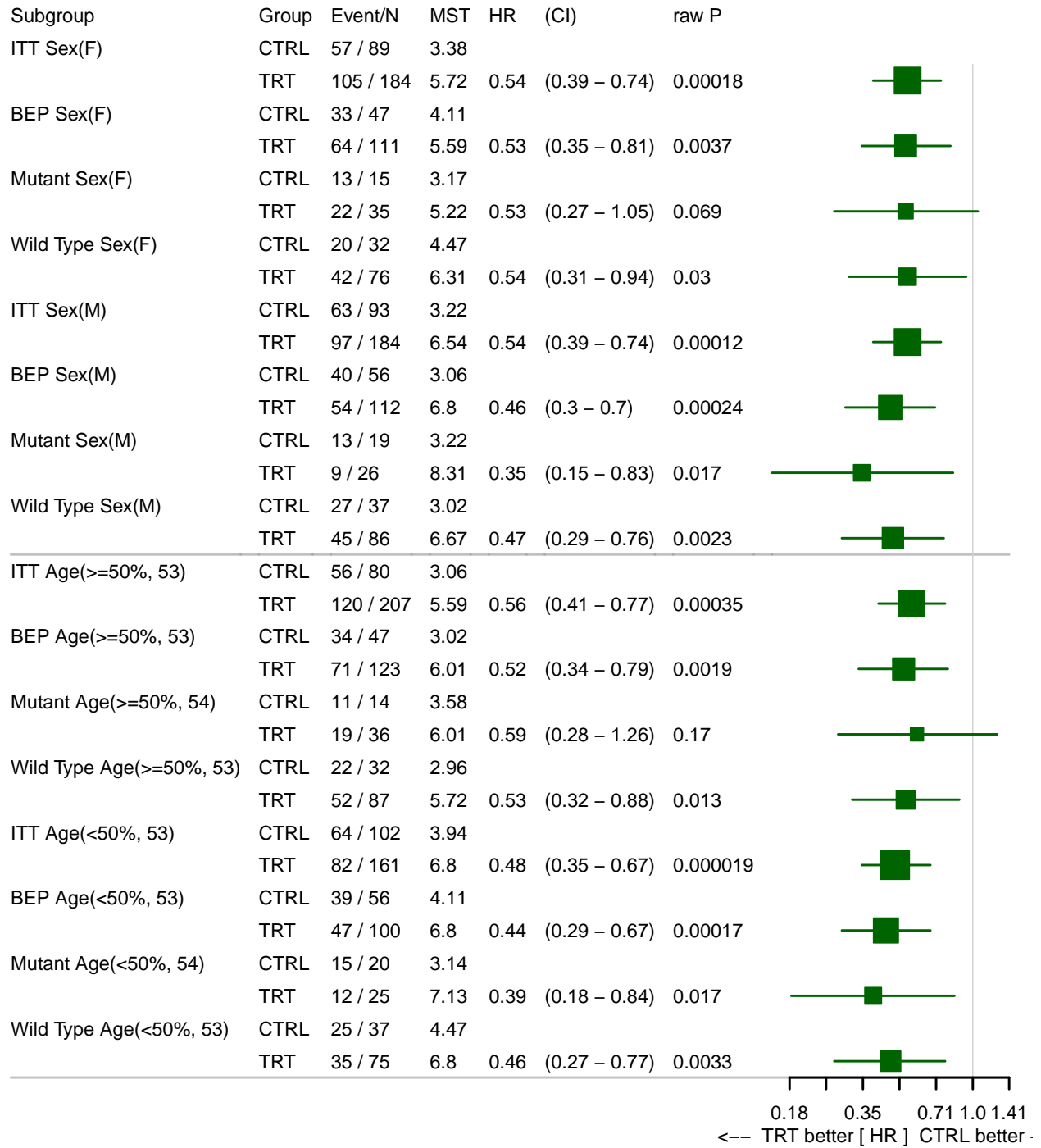


If bep column is not defined, the program will take the non NA entries in subgroups column as BEP

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS", "PFS.event"),
                    trt="Arm",
                    var=c("Sex", "Age"), compare.bep.itt=FALSE,
                    compare.subgroup=TRUE, subgroup="KRAS.mutant", show.itt=TRUE, show.bep=TRUE
                    )
```

show.bep is TRUE but bep is not specified, will define the non NA entries in subgroup column as BEP

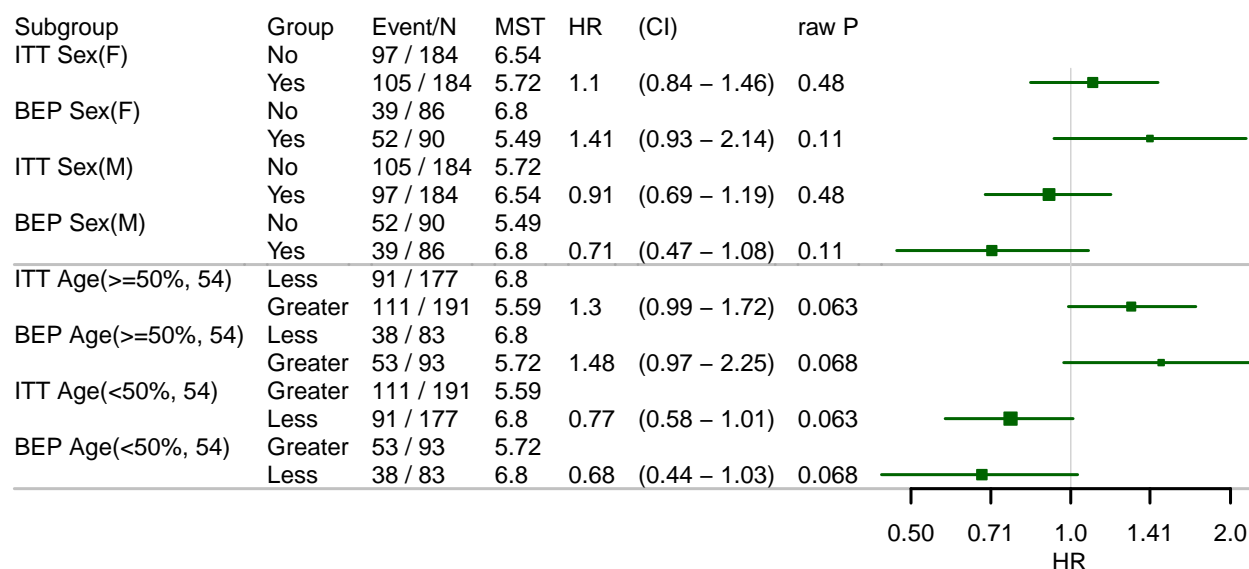
Across arm, Compare KRAS.mutant subgroup
PFS
Unadjusted, unstratified analysis



8.5 1-arm, compare ITT vs BEP

```
PlotTabForestMulti(data=subset(input,Arm=="TRT"),
                   outcome.class="survival",
                   outcome.var=c("PFS","PFS.event"),
                   trt=NULL,
                   var=c("Sex","Age"),
                   bep="BEP",bep.indicator=1, compare.bep.itt=TRUE
                   )
```

Within arm, Compare BEP vs. All PFS Unadjusted, unstratified analysis



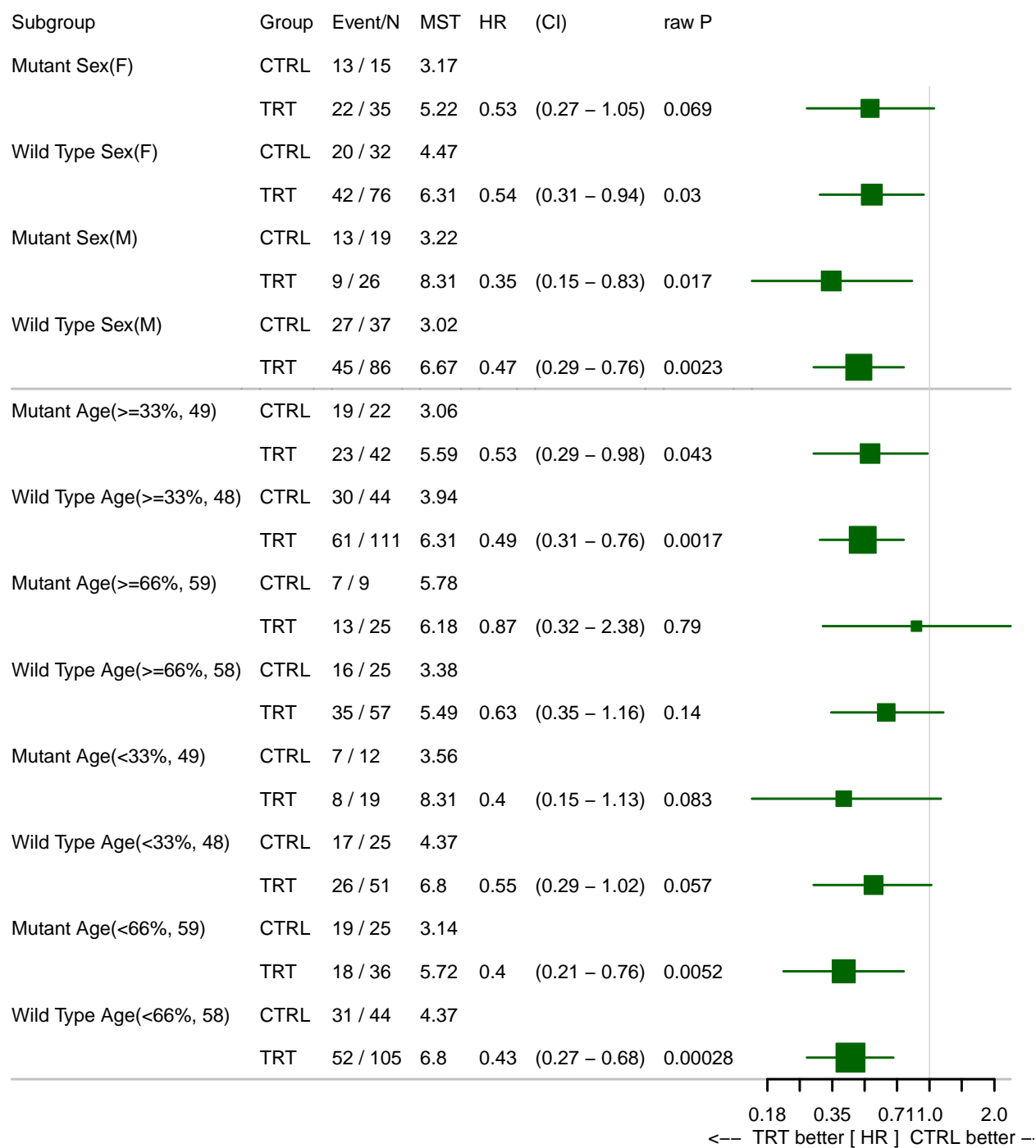
8.6 2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker

```
PlotTabForestMulti(data=input,
                   outcome.class="survival",
                   outcome.var=c("PFS","PFS.event"),
                   trt="Arm", percentile.cutoff=c(.33,.66),
                   var=c("Sex","Age"),
                   bep="BEP",bep.indicator=1, compare.bep.itt=FALSE,
                   compare.subgroup=TRUE, subgroup="KRAS.mutant"
                   )
```

Across arm, Compare KRAS.mutant subgroup

PFS

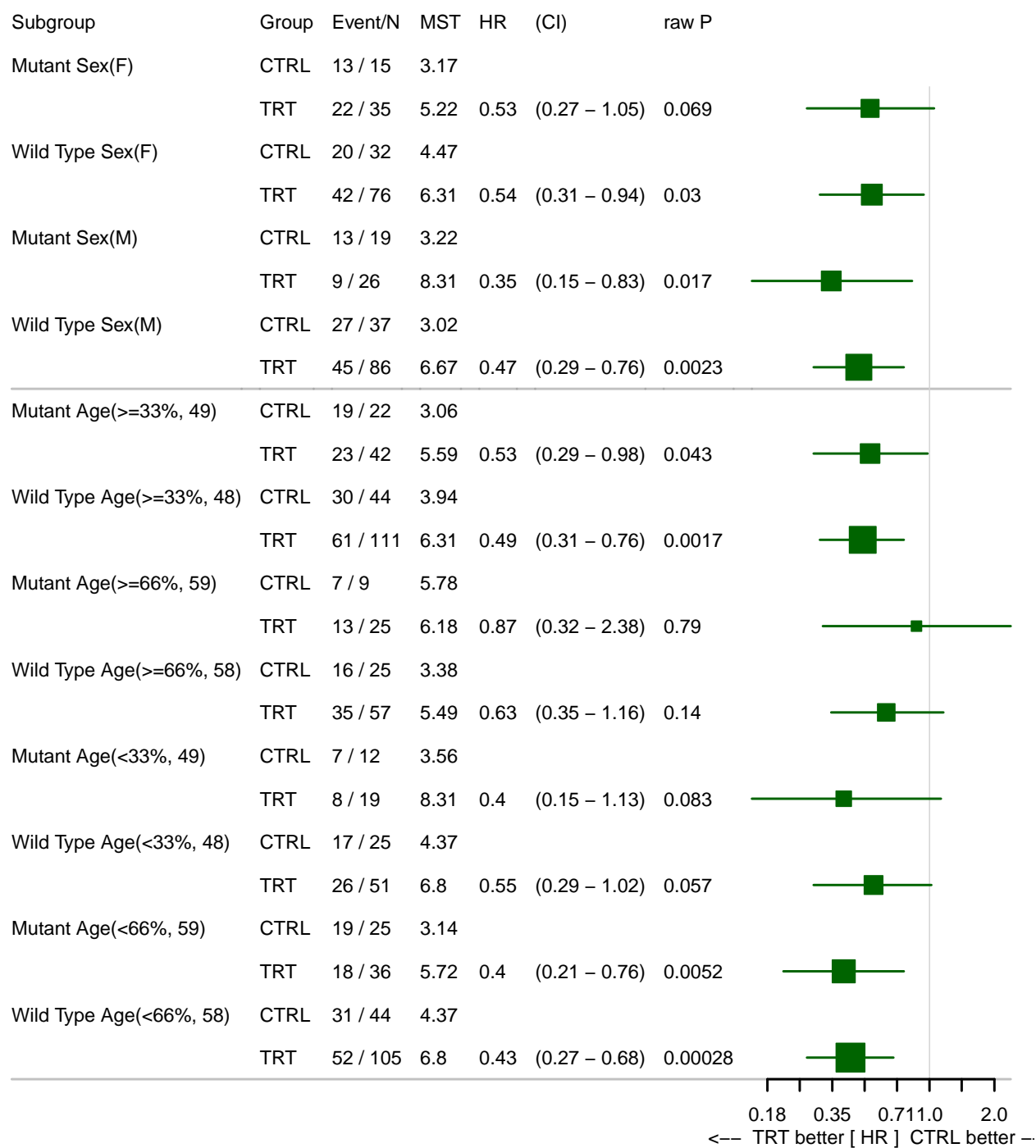
Unadjusted, unstratified analysis



8.7 2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker, calculate “< cutoff”

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS","PFS.event"),
                    trt="Arm", percentile.cutoff=c(.33,.66),less=TRUE,greater=FALSE,
                    var=c("Sex","Age"),
                    bep="BEP",bep.indicator=1, compare.bep.itc=FALSE,
                    compare.subgroup=TRUE, subgroup="KRAS.mutant"
                    )
```

Across arm, Compare KRAS.mutant subgroup
PFS
Unadjusted, unstratified analysis

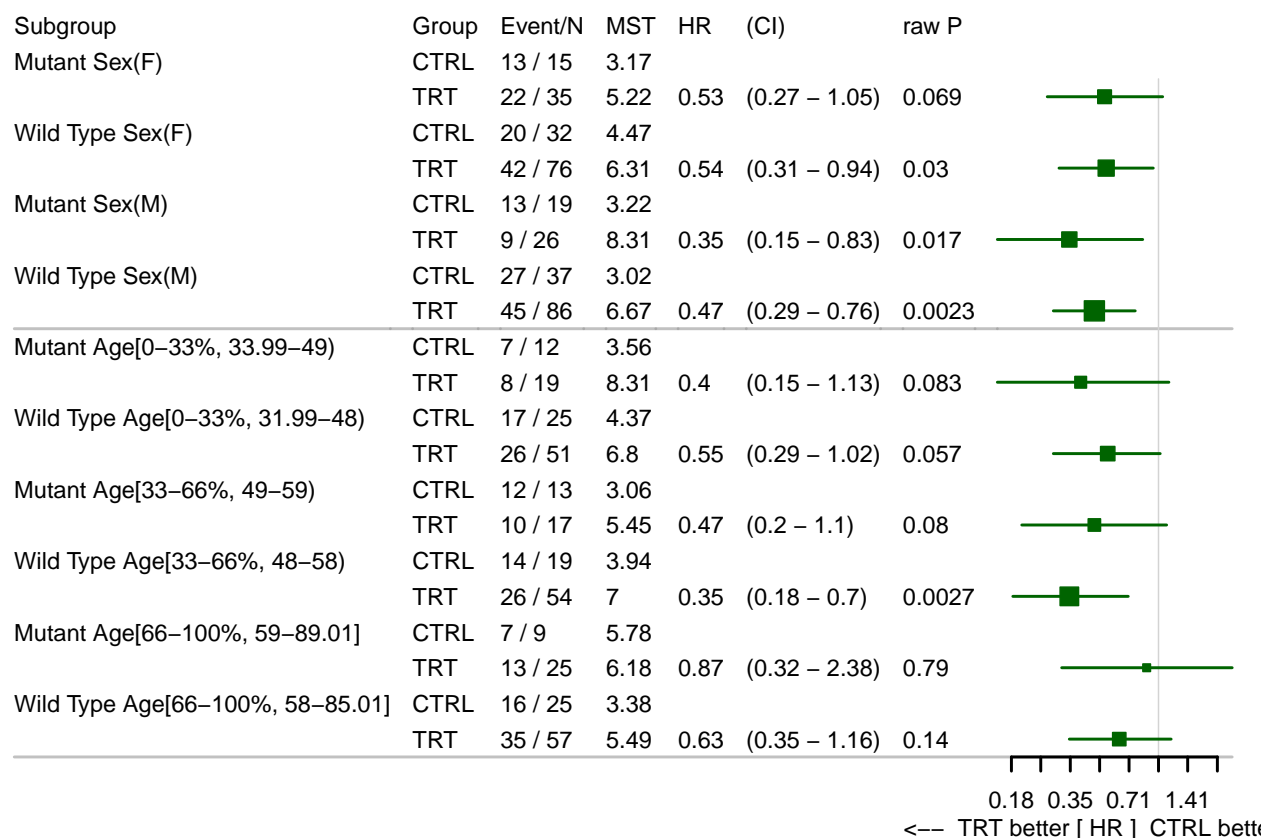


8.8 2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker, calculate within bin statistics

```
PlotTabForestMulti(data=input,
                   outcome.class="survival",
                   outcome.var=c("PFS","PFS.event"),
                   trt="Arm", percentile.cutoff=c(.33,.66),within.bin=TRUE,
                   var=c("Sex","Age"),
                   bep="BEP",bep.indicator=1, compare.bep.it=FALSE,
                   compare.subgroup=TRUE, subgroup="KRAS.mutant"
                   )
```

```
## within.bin is TRUE, greater and less will be ignored
## within.bin is TRUE, greater and less will be ignored
## within.bin is TRUE, greater and less will be ignored
## within.bin is TRUE, greater and less will be ignored
```

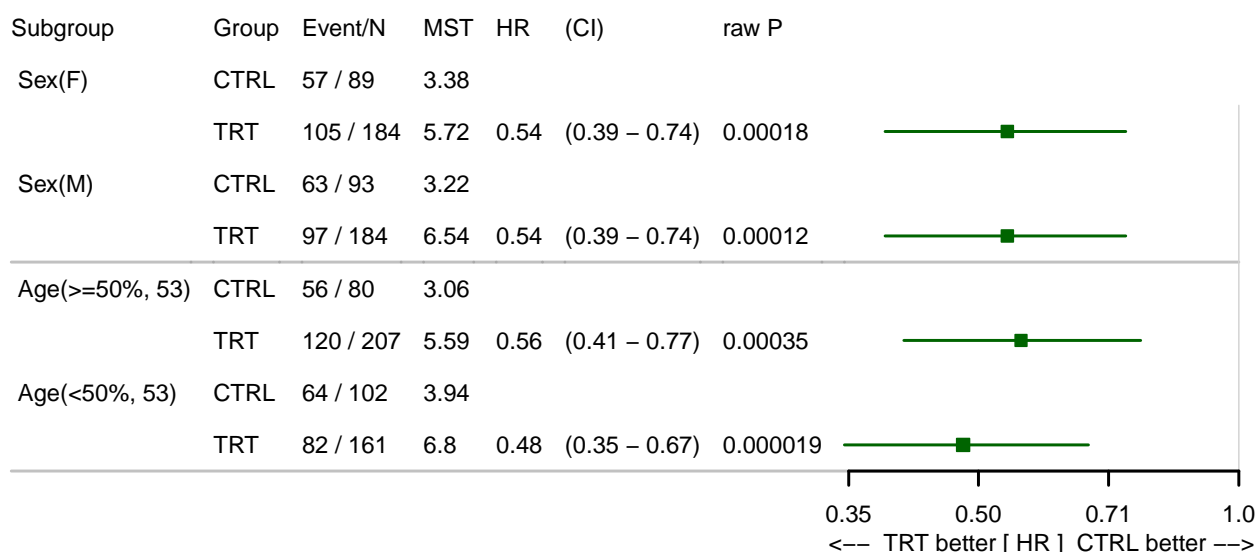
Across arm, Compare KRAS.mutant subgroup PFS Unadjusted, unstratified analysis



8.9 Basic forest plot without comparison

```
PlotTabForestMulti(data=input,
                    outcome.class="survival",
                    outcome.var=c("PFS","PFS.event"),
                    trt="Arm",
                    var=c("Sex","Age"),
                    compare.bep.itt=FALSE, compare.subgroup=FALSE,itt.name=""
                    )
```

Across arm PFS Unadjusted, unstratified analysis

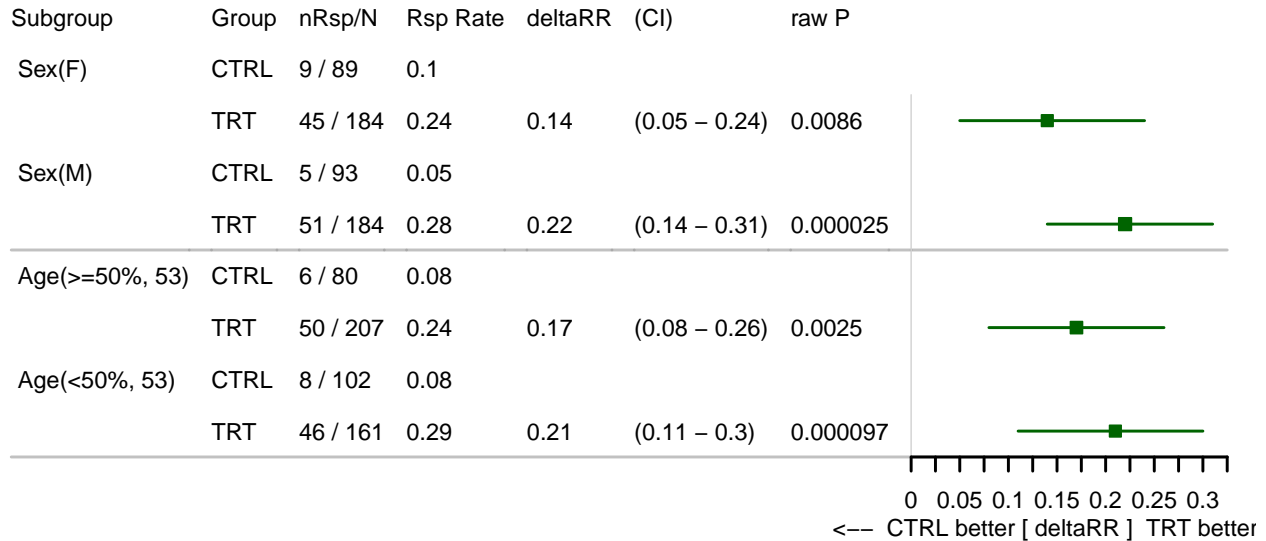


8.10 Response outcome

```
PlotTabForestMulti(data=input,
                    outcome.class="binary",
                    outcome.var=c("Response"),
                    rsp.cat = TRUE,
                    rsp.response = c("CR","PR"),
                    rsp.nonresponse = c("SD", "PD","NON CR/PD","NE",NA),
                    trt="Arm",
                    var=c("Sex","Age"),
                    compare.bep.itt=FALSE, compare.subgroup=FALSE,itt.name=""
                    )
```

```
## Covariate adjustment and stratification are not supported for binary outcome
## Covariate adjustment and stratification are not supported for binary outcome
```

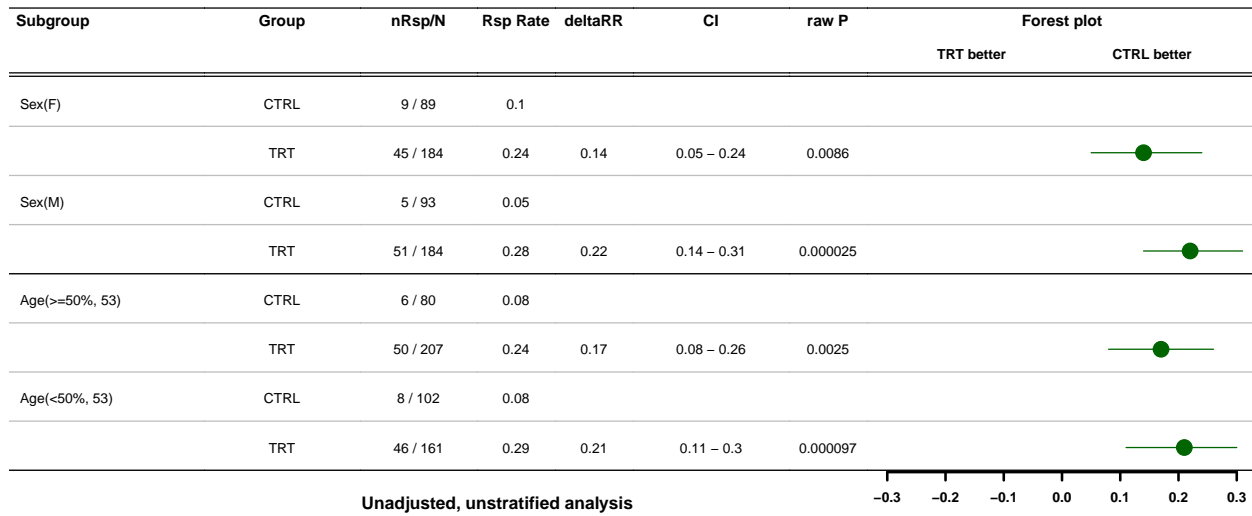
**Across arm
Response
Unadjusted, unstratified analysis**



```
PlotTabForestMulti(data=input,
                    outcome.class="binary",
                    outcome.var=c("Response"),
                    rsp.cat = TRUE,
                    rsp.response = c("CR", "PR"),
                    rsp.nonresponse = c("SD", "PD", "NON CR/PD", "NE", NA),
                    trt="Arm",
                    var=c("Sex", "Age"),
                    compare.bep.itt=FALSE, compare.subgroup=FALSE, itt.name="", tabforest=T
)
```

```
## Covariate adjustment and stratification are not supported for binary outcome
## Covariate adjustment and stratification are not supported for binary outcome
```

Across arm Response

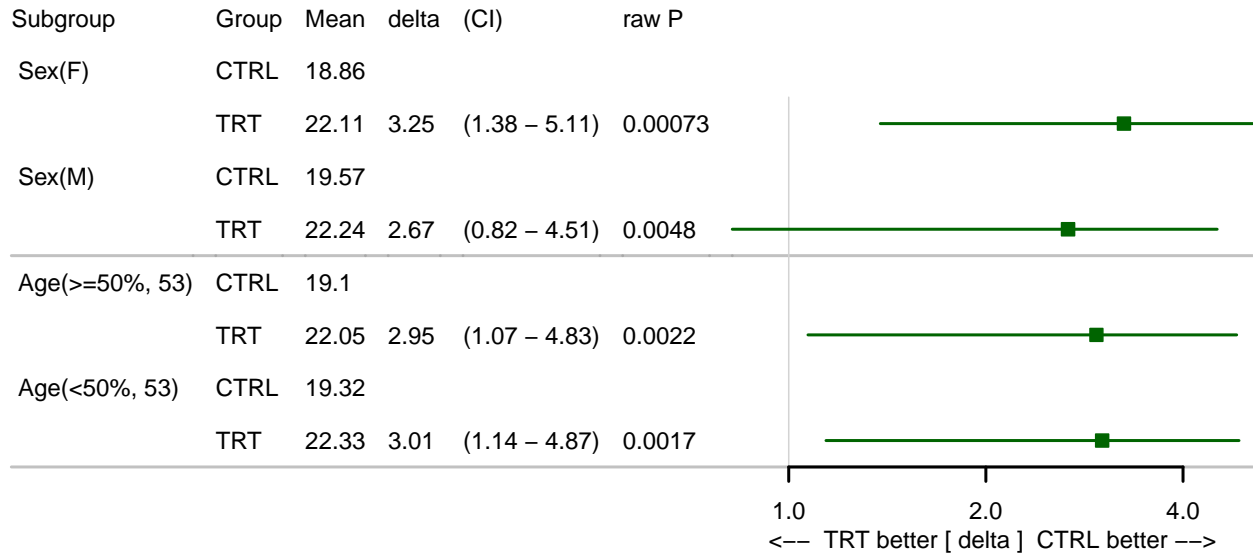


8.11 Continuous endpoint

```
PlotTabForestMulti(data=input,
                    outcome.class="continuous",
                    outcome.var=c("Lab_ontrt"),
                    trt="Arm",
                    var=c("Sex", "Age"),
                    compare.bep.itt=FALSE, compare.subgroup=FALSE, itt.name=""
                    )
```

```
## Stratification is not supported for continuous outcome
## Stratification is not supported for continuous outcome
```

Across arm
Lab_ontrt
Unadjusted, unstratified analysis

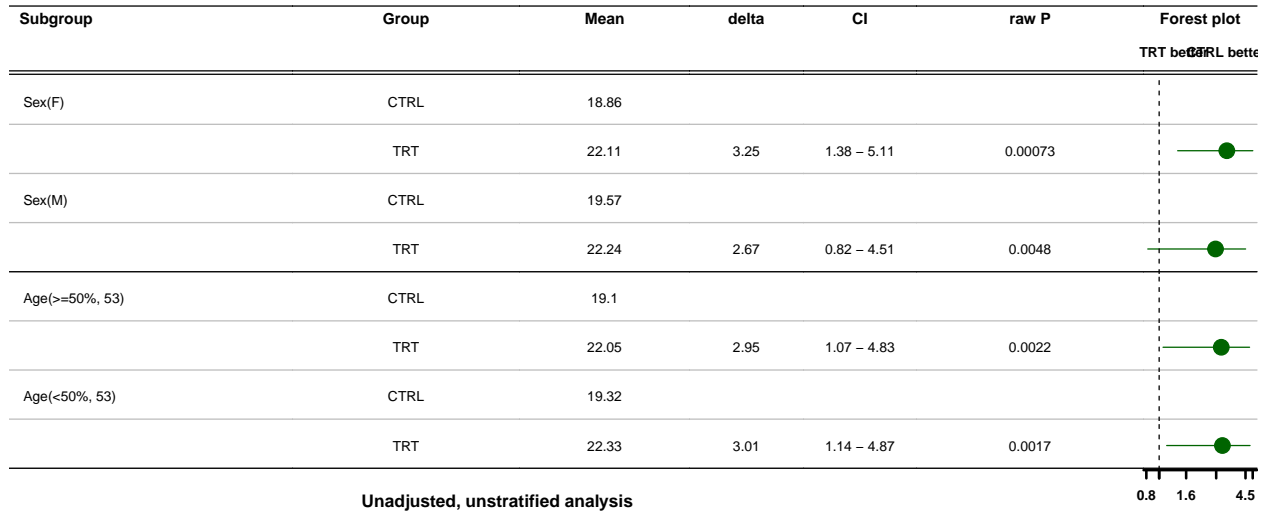


```
PlotTabForestMulti(data=input,
  outcome.class="continuous",
  outcome.var=c("Lab_ontrt"),
  trt="Arm",
  var=c("Sex", "Age"),
  compare.bep.itt=FALSE, compare.subgroup=FALSE, itt.name="", tabforest=T
)
```

```
## Stratification is not supported for continuous outcome
## Stratification is not supported for continuous outcome
```

```
## Warning in log(clip): NaNs produced
```

Across arm Lab_ontrt



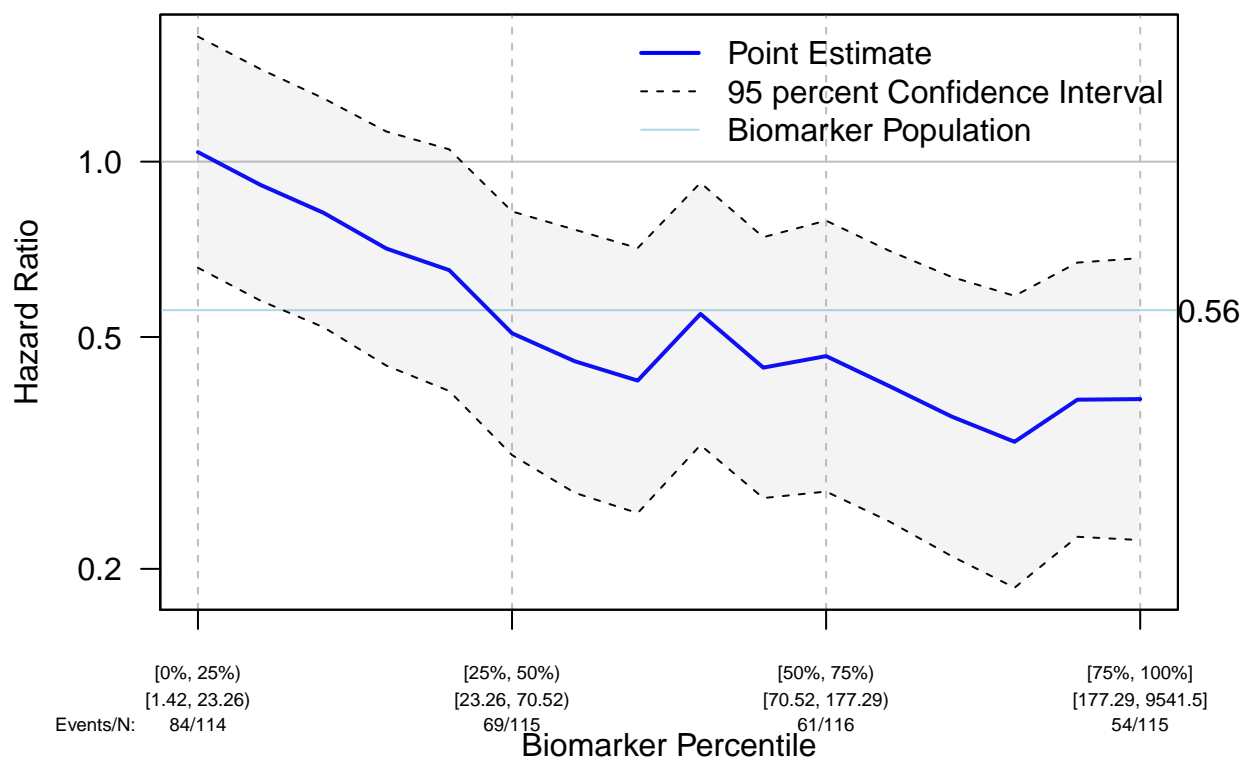
9 PlotSTEPP(): STEPP (Subpopulation Treatment Effect Pattern Plot) from the given point estimates and confidence intervals at desired percentiles.

9.1 Survival outcome

```
PlotSTEPP(data = input,
  outcome.var = c("PFS", "PFS.event"),
  outcome.class = "survival",
  trt = "Arm",
  var = "KRAS.exprs",
  placebo.code = "CTRL",
  active.code = "TRT",
  csv.name = NULL,
  pdf.name = NULL
)
```

some NA in var column, will ignore NA entries

STEPP: Subgroup Treatment Effect Pattern Plot



##	Window	Center	Hazard Ratio	CI Lower	CI Upper	BM Lower	BM Upper	
##	[1,]	0.125	1.0382905	0.6576013	1.6393629	1.42	23.26	
##	[2,]	0.175	0.9116623	0.5769829	1.4404727	5.98	32.00	
##	[3,]	0.225	0.8168277	0.5196594	1.2839325	9.51	42.81	
##	[4,]	0.275	0.7091655	0.4465512	1.1262218	14.03	48.84	
##	[5,]	0.325	0.6512376	0.4040444	1.0496628	19.70	59.30	
##	[6,]	0.375	0.5074886	0.3136041	0.8212413	23.26	70.52	
##	[7,]	0.425	0.4542622	0.2700666	0.7640860	32.00	77.71	
##	[8,]	0.475	0.4208886	0.2493019	0.7105732	42.81	95.01	
##	[9,]	0.525	0.5477689	0.3262293	0.9197544	48.84	121.94	
##	[10,]	0.575	0.4430307	0.2645633	0.7418874	59.30	151.17	
##	[11,]	0.625	0.4636518	0.2714610	0.7919111	70.52	177.29	
##	[12,]	0.675	0.4121338	0.2414306	0.7035327	77.71	213.78	
##	[13,]	0.725	0.3650580	0.2102587	0.6338257	95.01	259.57	
##	[14,]	0.775	0.3304610	0.1856466	0.5882385	121.94	317.37	
##	[15,]	0.825	0.3903051	0.2270411	0.6709713	151.17	467.88	
##	[16,]	0.875	0.3912302	0.2241152	0.6829571	177.29	9541.50	
##	BM	Center	Window	Left	Window	Right	N	Events
##	[1,]	11.010		0.00		0.25	114	84
##	[2,]	16.450		0.05		0.30	115	84
##	[3,]	21.860		0.10		0.35	115	85
##	[4,]	27.860		0.15		0.40	115	78
##	[5,]	36.250		0.20		0.45	115	73
##	[6,]	45.250		0.25		0.50	115	69
##	[7,]	53.265		0.30		0.55	114	59
##	[8,]	64.450		0.35		0.60	115	59
##	[9,]	73.010		0.40		0.65	115	63

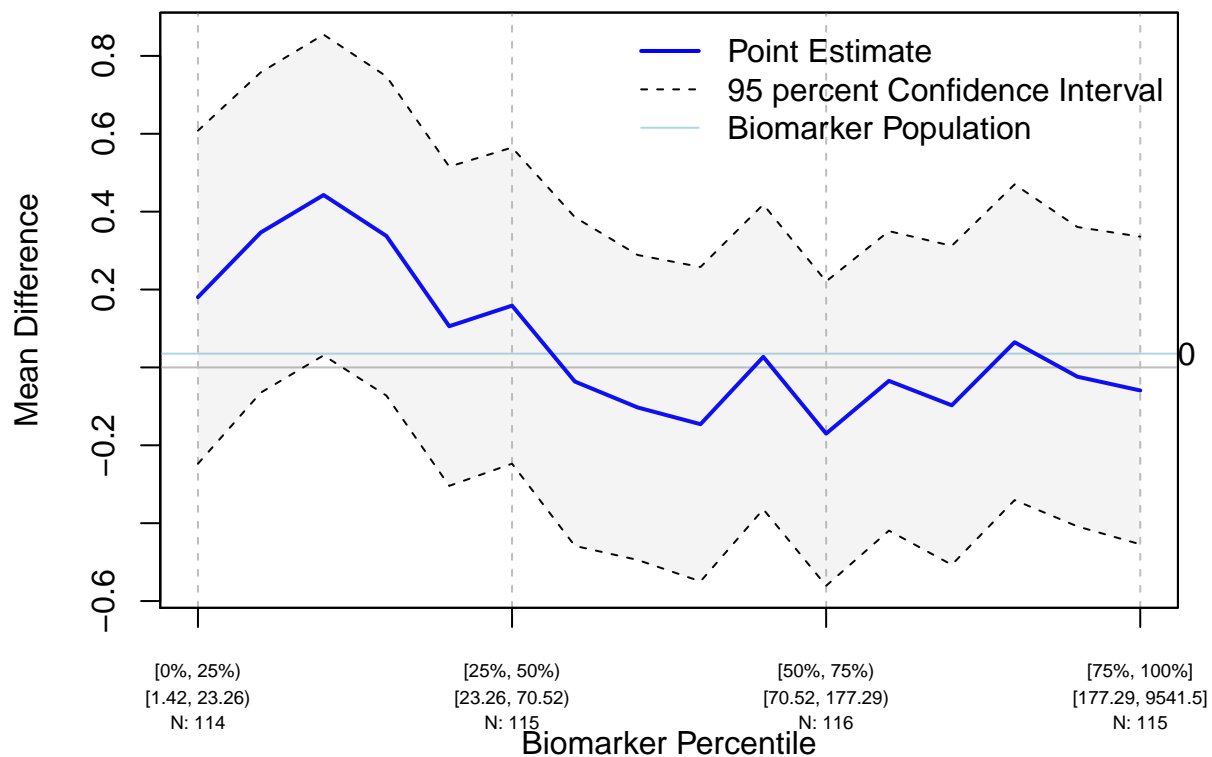
```
## [10,]    88.030      0.45      0.70 115    62
## [11,]   101.480      0.50      0.75 116    61
## [12,]   133.900      0.55      0.80 116    61
## [13,]   165.420      0.60      0.85 115    55
## [14,]   195.360      0.65      0.90 115    51
## [15,]   238.860      0.70      0.95 115    56
## [16,]   292.040      0.75      1.00 115    54
```

9.2 Continuous outcome

```
PlotSTEPP(data = input,
  outcome.var = "Baseline.SLD",
  outcome.class = "continuous",
  trt = "Arm",
  var = "KRAS.exprs",
  covariate= "Sex",
  placebo.code = "CTRL",
  active.code = "TRT",
  csv.name = NULL,
  pdf.name = NULL
)
```

```
## some NA in var column, will ignore NA entries
```

STEPP: Subgroup Treatment Effect Pattern Plot



```
## Window Center Mean Difference CI Lower CI Upper BM Lower
```

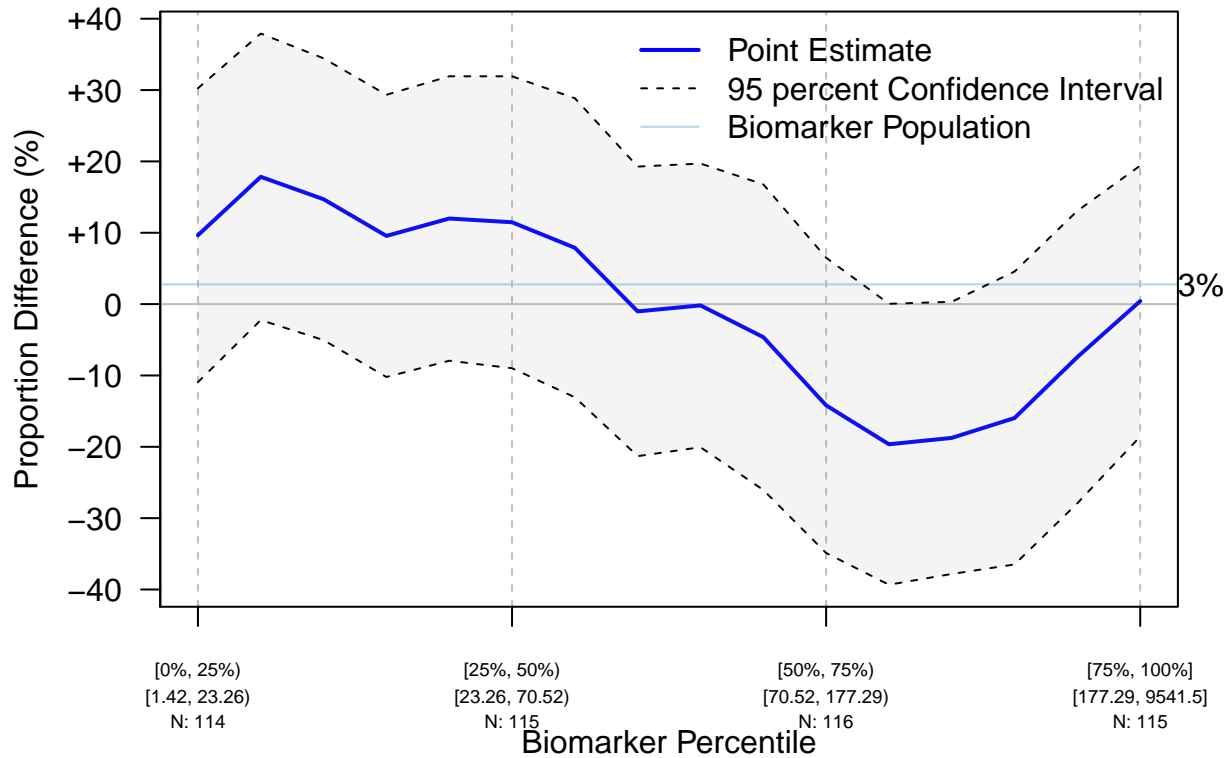
```
## [1,]      0.125      0.18035575 -0.24729997 0.6080115      1.42
## [2,]      0.175      0.34651479 -0.06475305 0.7577826      5.98
## [3,]      0.225      0.44278821  0.03092580 0.8546506      9.51
## [4,]      0.275      0.33749063 -0.07236992 0.7473512     14.03
## [5,]      0.325      0.10572728 -0.30412158 0.5155761     19.70
## [6,]      0.375      0.15866042 -0.24724256 0.5645634     23.26
## [7,]      0.425     -0.03630432 -0.45831952 0.3857109     32.00
## [8,]      0.475     -0.10286329 -0.49436652 0.2886399     42.81
## [9,]      0.525     -0.14583073 -0.54953031 0.2578689     48.84
## [10,]     0.575      0.02704796 -0.36419706 0.4182930     59.30
## [11,]     0.625     -0.16994763 -0.56071364 0.2208184     70.52
## [12,]     0.675     -0.03456171 -0.41907553 0.3499521     77.71
## [13,]     0.725     -0.09734050 -0.50684711 0.3121661     95.01
## [14,]     0.775      0.06465414 -0.34072771 0.4700360    121.94
## [15,]     0.825     -0.02383926 -0.40821143 0.3605329    151.17
## [16,]     0.875     -0.05926090 -0.45420790 0.3356861    177.29
##      BM Upper BM Center Window Left Window Right      N
## [1,]    23.26    11.010      0.00      0.25 114
## [2,]    32.00    16.450      0.05      0.30 115
## [3,]    42.81    21.860      0.10      0.35 115
## [4,]    48.84    27.860      0.15      0.40 115
## [5,]    59.30    36.250      0.20      0.45 115
## [6,]    70.52    45.250      0.25      0.50 115
## [7,]    77.71    53.265      0.30      0.55 114
## [8,]    95.01    64.450      0.35      0.60 115
## [9,]   121.94    73.010      0.40      0.65 115
## [10,]   151.17    88.030      0.45      0.70 115
## [11,]   177.29   101.480      0.50      0.75 116
## [12,]   213.78   133.900      0.55      0.80 116
## [13,]   259.57   165.420      0.60      0.85 115
## [14,]   317.37   195.360      0.65      0.90 115
## [15,]   467.88   238.860      0.70      0.95 115
## [16,]  9541.50   292.040      0.75      1.00 115
```

9.3 Binary outcome variable

```
PlotSTEPP(data = input,
  outcome.var = "ECOG",
  outcome.class = "binary",
  trt = "Arm",
  var = "KRAS.exprs",
  placebo.code = "CTRL",
  active.code = "TRT",
  csv.name = NULL,
  pdf.name = NULL
)
```

```
## some NA in var column, will ignore NA entries
```

STEPP: Subgroup Treatment Effect Pattern Plot



##	Window	Center	Proportion	Difference	CI Lower	CI Upper	
##	[1,]	0.125		0.096558637	-0.10936788	0.3024851571	
##	[2,]	0.175		0.178408350	-0.02235039	0.3791670900	
##	[3,]	0.225		0.147000659	-0.05041839	0.3444197101	
##	[4,]	0.275		0.095583388	-0.10218602	0.2933527961	
##	[5,]	0.325		0.119973632	-0.07934753	0.3192947989	
##	[6,]	0.375		0.114700066	-0.08986157	0.3192616985	
##	[7,]	0.425		0.078947368	-0.13057600	0.2884707407	
##	[8,]	0.475		-0.010179010	-0.21308461	0.1927265895	
##	[9,]	0.525		-0.001808318	-0.20059338	0.1969767445	
##	[10,]	0.575		-0.046292948	-0.26043294	0.1678470400	
##	[11,]	0.625		-0.141906874	-0.34878874	0.0649749952	
##	[12,]	0.675		-0.196428571	-0.39328032	0.0004231801	
##	[13,]	0.725		-0.187500000	-0.37820558	0.0032055783	
##	[14,]	0.775		-0.159638554	-0.36486679	0.0455896813	
##	[15,]	0.825		-0.074191280	-0.27905945	0.1306768944	
##	[16,]	0.875		0.004219409	-0.18560507	0.1940438921	
##	BM Lower	BM Upper	BM Center	Window	Left	Window Right	N
##	[1,]	1.42	23.26	11.010	0.00	0.25	114
##	[2,]	5.98	32.00	16.450	0.05	0.30	115
##	[3,]	9.51	42.81	21.860	0.10	0.35	115
##	[4,]	14.03	48.84	27.860	0.15	0.40	115
##	[5,]	19.70	59.30	36.250	0.20	0.45	115
##	[6,]	23.26	70.52	45.250	0.25	0.50	115
##	[7,]	32.00	77.71	53.265	0.30	0.55	114
##	[8,]	42.81	95.01	64.450	0.35	0.60	115
##	[9,]	48.84	121.94	73.010	0.40	0.65	115

```
## [10,]    59.30   151.17    88.030         0.45         0.70 115
## [11,]    70.52   177.29   101.480         0.50         0.75 116
## [12,]    77.71   213.78   133.900         0.55         0.80 116
## [13,]    95.01   259.57   165.420         0.60         0.85 115
## [14,]   121.94   317.37   195.360         0.65         0.90 115
## [15,]   151.17   467.88   238.860         0.70         0.95 115
## [16,]   177.29  9541.50   292.040         0.75         1.00 115
```

10 CoxTab(): fit cox proportional model for multiple covariates (additive model or separate models)

10.1 single covariate

```
CoxTab(data=sample.data, tte="OS", cens="OS.event", bep='BEP', var='Sex' )
```

```
##           HR      CI.low CI.high p-value n.trt n.ref
## Sex (M/F) "0.85" "0.42" "1.72"  "0.65"  "128" "129"
```

10.2 multiple covariates, ITT

Additive model will be fitted.

```
kable(
CoxTab(data=sample.data, tte="OS", cens="OS.event", var=c('Sex', "Country", "Age"),
  var.class=c("categorical", "categorical", "numeric"))
)
```

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Sex (M/F)	0.72	0.48	1.08	0.11	277	273
Country (USA/Other)	0.65	0.36	1.2	0.17	127	198
Country (Western Europe/Other)	0.77	0.5	1.2	0.24	225	198
Age	1.01	0.99	1.03	0.43		

Simplify: automatically learn var.class from column class:

```
kable(
CoxTab(data=sample.data, tte="OS", cens="OS.event", var=c('Sex', "Country", "Age"))
)
```

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Sex (M/F)	0.72	0.48	1.08	0.11	277	273
Country (USA/Other)	0.65	0.36	1.2	0.17	127	198
Country (Western Europe/Other)	0.77	0.5	1.2	0.24	225	198
Age	1.01	0.99	1.03	0.43		

10.3 BEP

```
kable(  
CoxTab(data=sample.data,tte="OS", cens="OS.event", var=c('Sex',"Country","Age"),  
       var.class=c("categorical","categorical","numeric"), bep="BEP")  
)
```

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Sex (M/F)	0.85	0.42	1.73	0.65	128	129
Country (USA/Other)	1.17	0.4	3.38	0.77	76	57
Country (Western Europe/Other)	1.11	0.44	2.83	0.83	124	57
Age	1.01	0.98	1.04	0.48		

10.4 Reorder Sex: M as reference

```
kable(  
CoxTab(data=sample.data,tte="OS", cens="OS.event", var=c('Sex',"Country","Age"),  
       var.class=c("ordered.factor","categorical","numeric"),  
       ordered.factor.levels=list(Sex=c("M","F")),bep="BEP")  
)
```

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Sex (F/M)	1.12	0.68	1.85	0.65	129	128
Country (USA/Other)	1.17	0.4	3.38	0.77	76	57
Country (Western Europe/Other)	1.11	0.44	2.83	0.83	124	57
Age	1.01	0.98	1.04	0.48		

10.5 Fit separate models for each variable instead of fitting an additive model

```
kable(  
CoxTab(data=sample.data,tte="OS", cens="OS.event", var=c('Sex',"Country","Age"),  
       additive=FALSE)  
)
```

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Sex (M/F)	0.71	0.48	1.07	0.099	277	273
Country (USA/Other)	0.67	0.37	1.22	0.19	127	198
Country (Western Europe/Other)	0.77	0.5	1.2	0.25	225	198
Age	1.01	0.99	1.02	0.54		

11 SummaryTwoGroups()

11.1 Continuous outcome

11.1.1 Create summary statistics

```
SummaryTwoGroups(outcome.var = input$OS, treatment.var = input$Arm,  
  placebo.code = "CTRL", active.code = "TRT",  
  outcome.class = "continuous")
```

```
## Effect.Size      Lower      Upper      P Mean.Placebo  
## 0.79113129 0.19464513 1.38761744 0.00942898 5.77854999  
## Mean.Active  
## 6.56968128
```

11.1.2 Add a covariate variable

```
SummaryTwoGroups(outcome.var = input$OS, treatment.var = input$Arm,  
  placebo.code = "CTRL", active.code = "TRT",  
  outcome.class = "continuous", covariate.var = input$Sex)
```

```
## Effect.Size      Lower      Upper      P Mean.Placebo  
## 0.795751256 0.199865806 1.391636707 0.008954882 5.563721382  
## Mean.Active  
## 6.359472638
```

11.1.3 Add return.fit = TRUE to return a table of summary statistics

```
SummaryTwoGroups(outcome.var = input$OS, treatment.var = input$Arm,  
  placebo.code = "CTRL", active.code = "TRT",  
  outcome.class = "continuous", covariate.var = input$Sex,  
  return.fit = TRUE)
```

```
## [[1]]  
## Effect.Size      Lower      Upper      P Mean.Placebo  
## 0.795751256 0.199865806 1.391636707 0.008954882 5.563721382  
## Mean.Active  
## 6.359472638  
##  
## [[2]]  
##  
## Call:  
## lm(formula = outcome.var[subgroup.var] ~ covariate.var[subgroup.var] +  
## treatment.var[subgroup.var])  
##  
## Coefficients:  
## (Intercept) covariate.var[subgroup.var]M  
## 5.5637 0.4204  
## treatment.var[subgroup.var]TRT  
## 0.7958
```

11.2 Binary outcome

11.2.1 Create summary statistics

```
SummaryTwoGroups(outcome.var = input$OS.event, treatment.var = input$Arm,  
                  placebo.code = "CTRL", active.code = "TRT",  
                  outcome.class = "binary")
```

```
## Effect.Size      Lower      Upper      P Rsp.Placebo  
## -0.04846512 -0.12251455  0.02558430  0.19901328  0.20879121  
## Rsp.Active     N.Placebo     N.Active nRsp.Placebo  nRsp.Active  
##  0.16032609 182.00000000 368.00000000  38.00000000  59.00000000
```

11.3 Survival variable

11.3.1 Create summary statistics

```
SummaryTwoGroups(outcome.var = input[, c("OS", "OS.event")],  
                  treatment.var = input$Arm, placebo.code = "CTRL",  
                  active.code = "TRT", outcome.class = "survival")
```

```
## CTRL.events      CTRL.n      CTRL.MST TRT.events      TRT.n      TRT.MST  
## 38.00000000 182.0000000 14.8829569 59.00000000 368.0000000 NA  
## Effect.Size      Lower      Upper      P  
##  0.6667451  0.4432032  1.0030365  0.0517253
```

11.3.2 Add a covariate variable

```
SummaryTwoGroups(outcome.var = input[, c("OS", "OS.event")],  
                  treatment.var = input$Arm, placebo.code = "CTRL",  
                  active.code = "TRT", outcome.class = "survival",  
                  covariate.var = input$Sex)
```

```
## CTRL.events      CTRL.n      CTRL.MST TRT.events      TRT.n  
## 38.00000000 182.0000000 14.88295688 59.00000000 368.00000000  
## TRT.MST Effect.Size      Lower      Upper      P  
## NA 0.63926120 0.42390908 0.96401541 0.03277593
```

11.3.3 Add a stratification variable

```
SummaryTwoGroups(outcome.var = input[, c("OS", "OS.event")],  
                  treatment.var = input$Arm, placebo.code = "CTRL",  
                  active.code = "TRT", outcome.class = "survival",  
                  covariate.var = input$Sex, strat.factor.var = input$Age)
```



```
## CTRL.events      CTRL.n      CTRL.MST  TRT.events      TRT.n
## 38.00000000 182.00000000 14.88295688 59.00000000 368.00000000
##      TRT.MST Effect.Size      Lower      Upper      P
##      NA      0.60116855  0.37830923  0.95531273  0.03128551
```

12 LogRankTab(): log rank test for subgroup analysis

```
kable(
  LogRankTab(data=input,tte="PFS",cens="PFS.event",var="Arm")
)
```

	CTRL	TRT
	N=182	N=368
Patients with event	120 (65.9%)	202 (54.9%)
Patients without event	62 (34.1%)	166 (45.1%)
Time to event (month)		
Median (KM)	3.25	5.82
95% CI Median	(2.83;4.14)	(5.49;6.8)
25% and 75%-ile	1.61;6.47	2.89;11.73
Range (inc. cens.)	0.03 to 12.32	0.03 to 13.8
p-value (Log-Rank Test)		0
Hazard Ratio		0.54
95% CI		(0.43;0.67)

13 BoxPlot(): advanced box plot function

13.1 Generate example dataset

```
example <- data.frame( y=c(rnorm(30)+10, rnorm(4)+20, rnorm(15)+15, NA),
  time=c(rep("t2", 30), rep("t4",4), rep("t1", 15), "t3"),
  grp=sample(1:3, 50, TRUE), sex=sample(1:2, 50, TRUE))
head(example)
```

```
##      y time grp sex
## 1  9.915827 t2  3  2
## 2 10.021031 t2  3  2
## 3 11.677153 t2  1  1
## 4 11.438670 t2  3  1
## 5 11.709963 t2  1  2
## 6 11.204036 t2  1  2
```

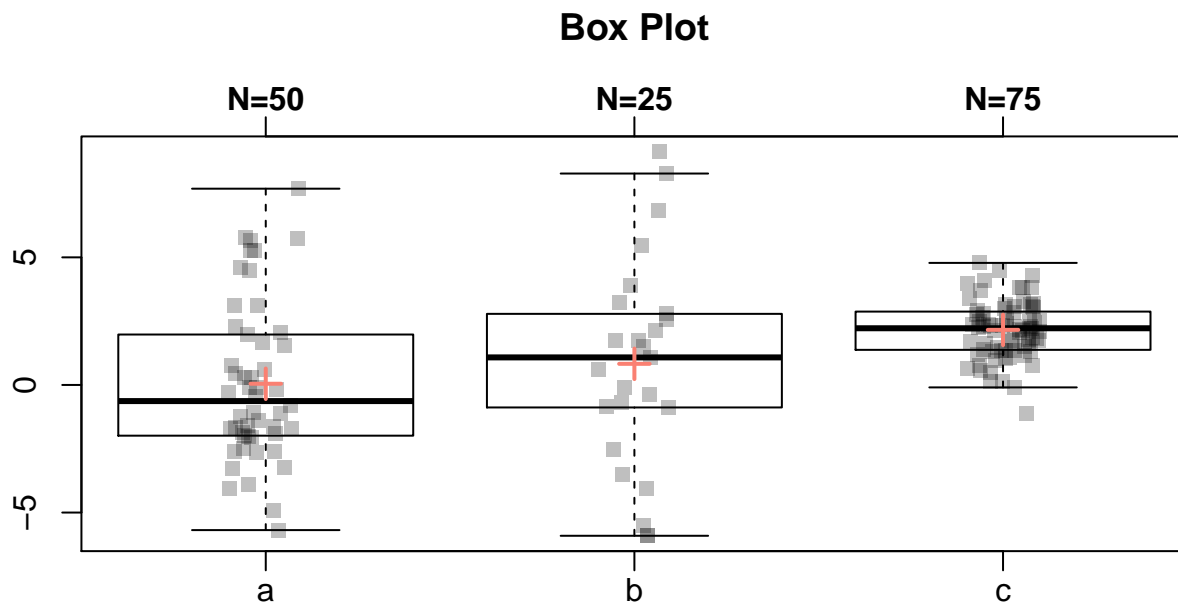
```
str(example)
```

```
## 'data.frame':  50 obs. of  4 variables:
## $ y : num  9.92 10.02 11.68 11.44 11.71 ...
## $ time: Factor w/ 4 levels "t1","t2","t3",...: 2 2 2 2 2 2 2 2 2 2 ...
```

```
## $ grp : int  3 3 1 3 1 1 2 3 2 3 ...
## $ sex : int  2 2 1 1 2 2 2 1 2 2 ...
```

13.2 Specify data as named list

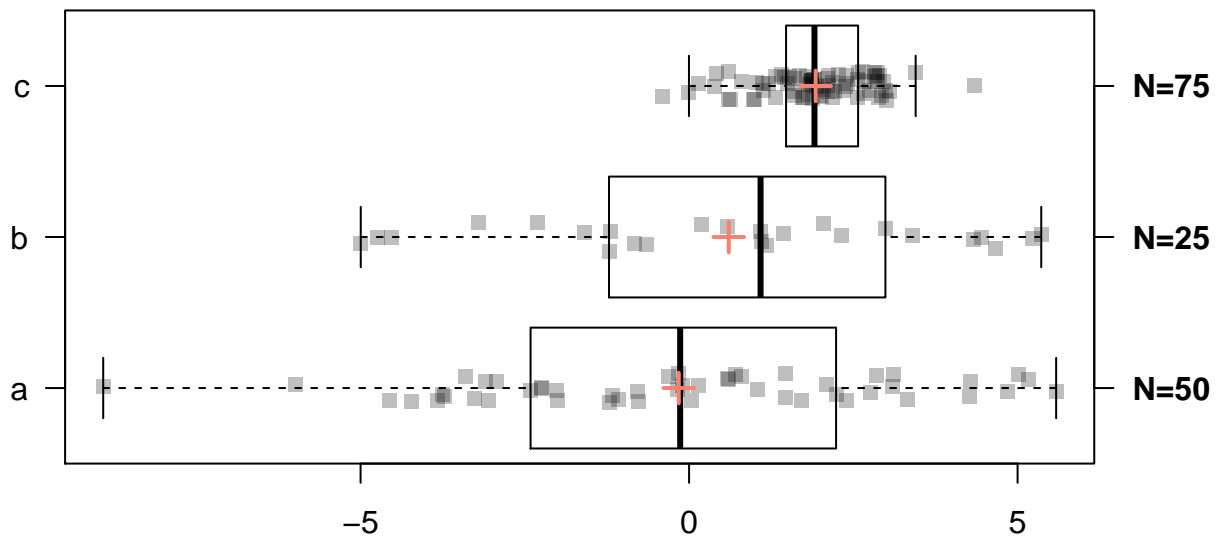
```
BoxPlot(list(a=rnorm(50,,3), b=rnorm(25,1,4), c=rnorm(75,2,1)))
```



13.3 Same plot, now horizontally plotted

```
BoxPlot(list(a=rnorm(50,,3), b=rnorm(25,1,4), c=rnorm(75,2,1)), horizontal=TRUE,
        Xaxis=list(las=2, hadj=2), Xaxis2=list(las=2, hadj=-.25))
```

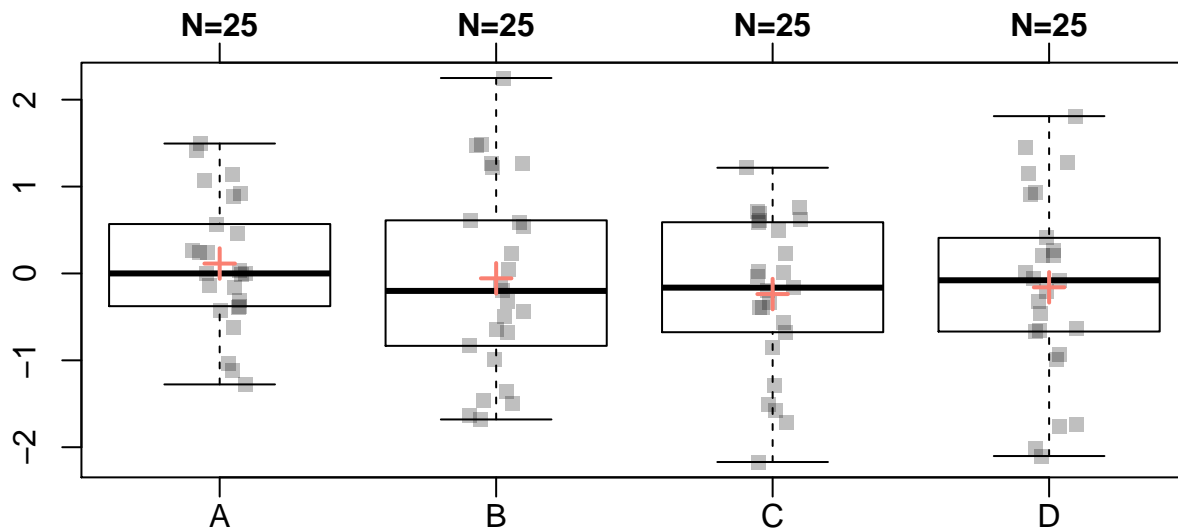
Box Plot



13.4 Specify data as numeric matrix

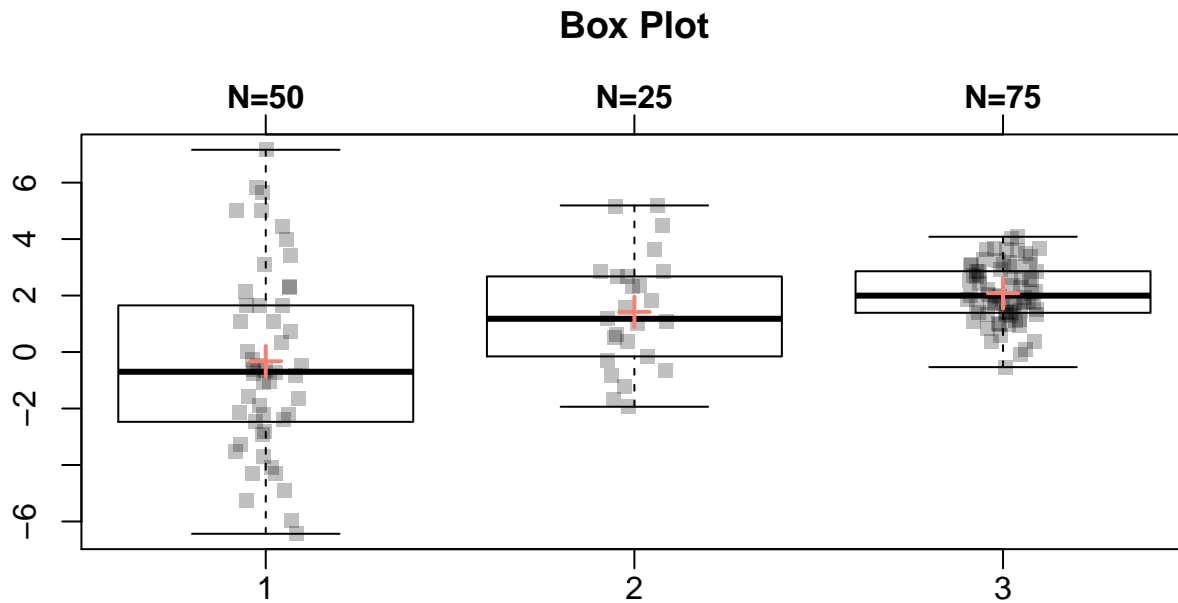
```
BoxPlot(matrix(rnorm(100), ncol=4, dimnames=list(NULL, LETTERS[1:4])) )
```

Box Plot



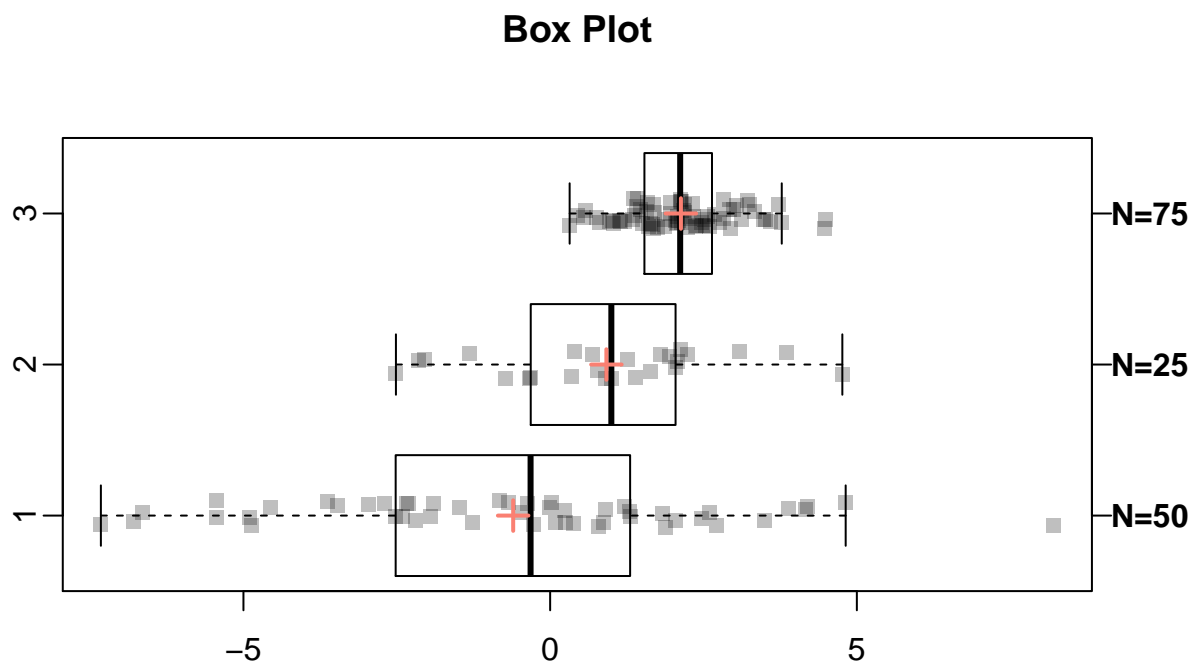
13.5 Specify data as numeric (unnamed) vectors

```
BoxPlot(rnorm(50,,3), rnorm(25,1,2), rnorm(75,2,1))
```



13.6 ... horizontally plotted (no axis-label rotation done here)

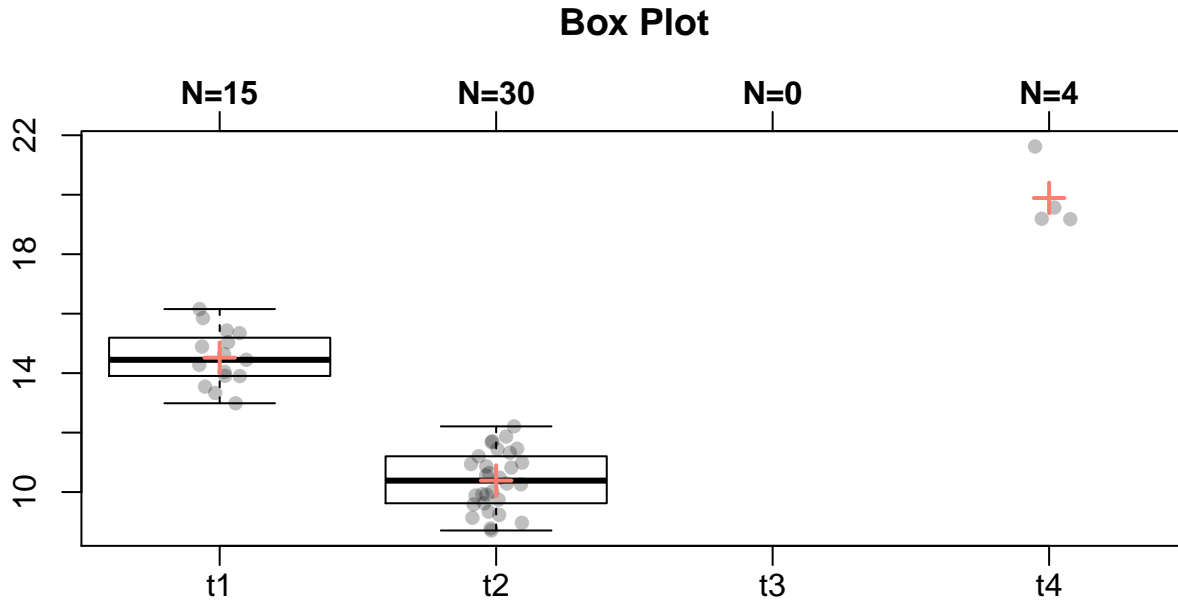
```
BoxPlot(rnorm(50,,3), rnorm(25,1,2), rnorm(75,2,1), horizontal=TRUE)
```



13.7 Plot values 'y' according to time 'time' (factor levels are automatically ordered as e.g. function sort does)

```
BoxPlot(example, y~time, sc.pch=16)
```

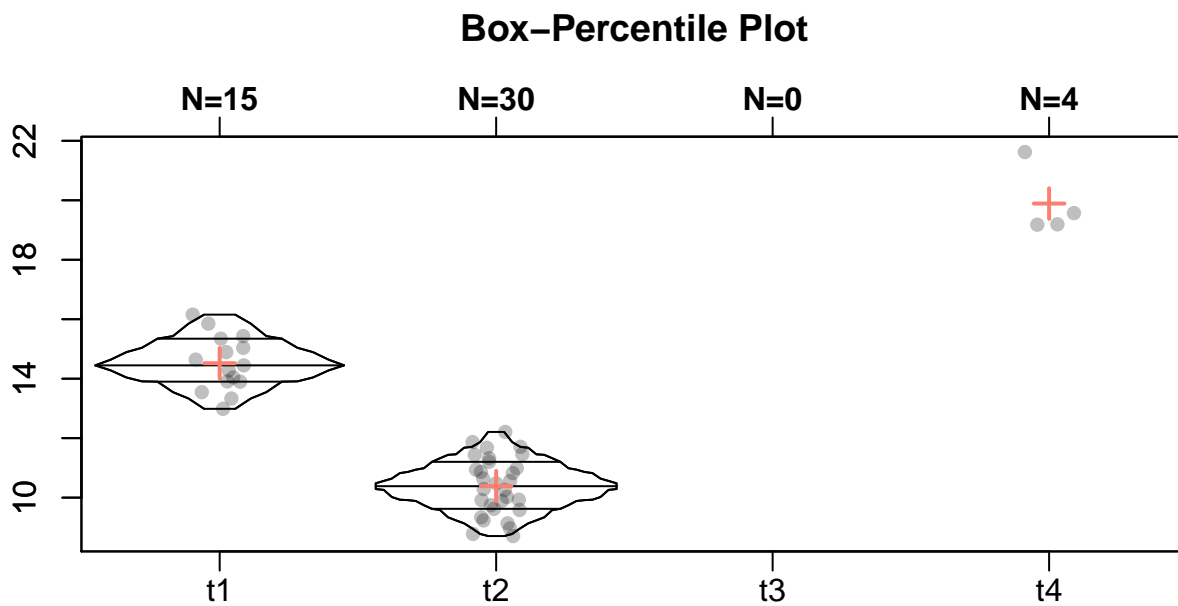
```
## Number of samples removed due to missing Y: 1
```



13.8 Now as box-percentile plot

```
BoxPlot(example, y~time, sc.pch=16, box.type="bp")
```

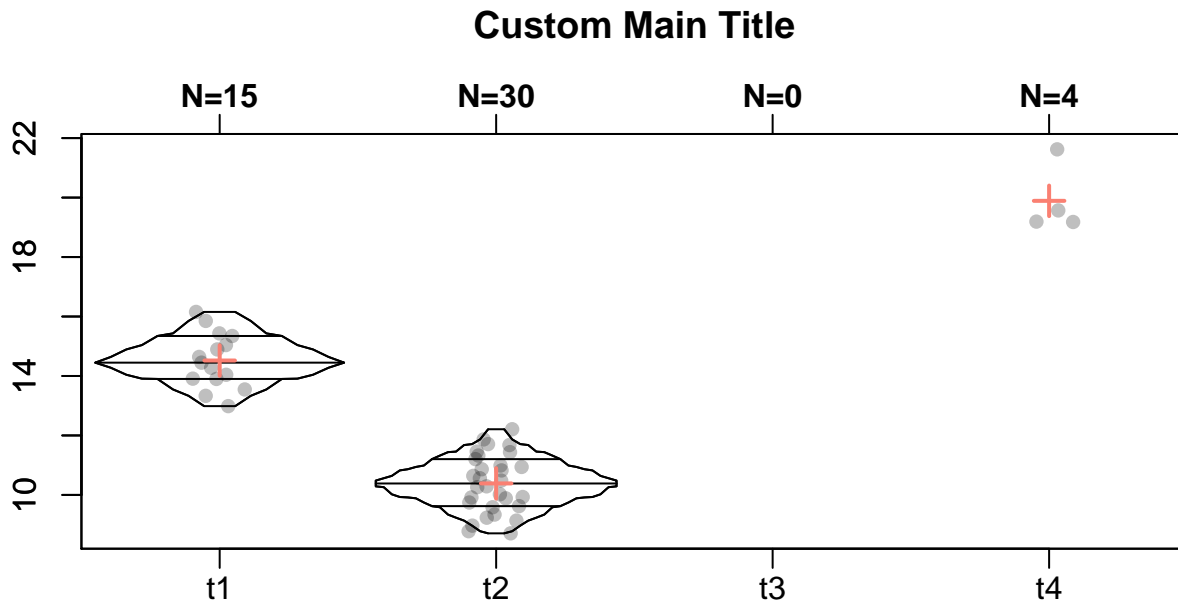
```
## Number of samples removed due to missing Y: 1
```



13.9 With custom main title

```
BoxPlot(example, y~time, sc.pch=16, box.type="bp", Title=list(main="Custom Main Title"))
```

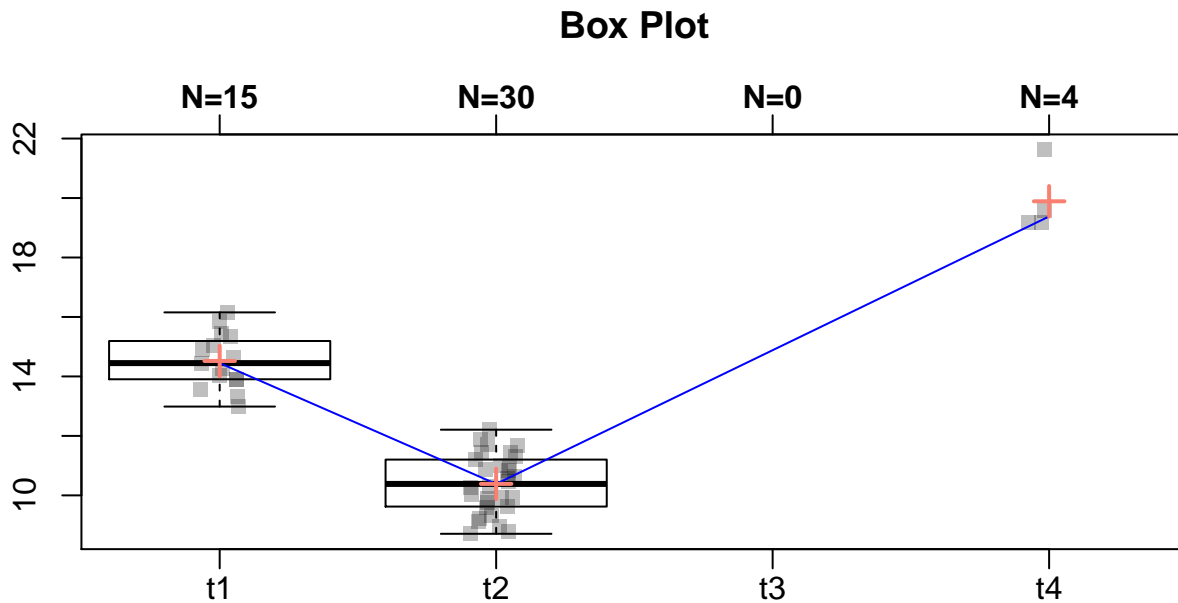
```
## Number of samples removed due to missing Y: 1
```



13.10 The same plot with trend line (connects either means or medians) and Y-axis label

```
BoxPlot(example, y~time, trend="median", ylab="Y-Axis Label")
```

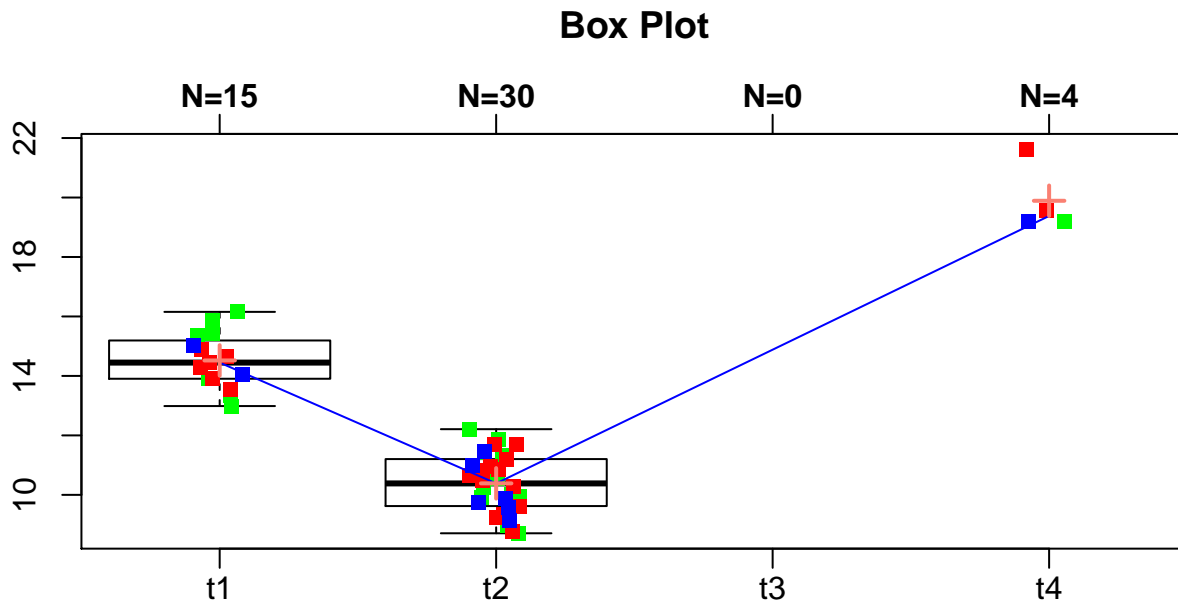
```
## Number of samples removed due to missing Y: 1
```



13.11 Use an addition grouping variable to color points in the stripchart

```
BoxPlot(example, y~time, trend="median", ylab="Y-Axis Label",
        sc.col=c("red", "blue", "green")[example$grp] )
```

Number of samples removed due to missing Y: 1

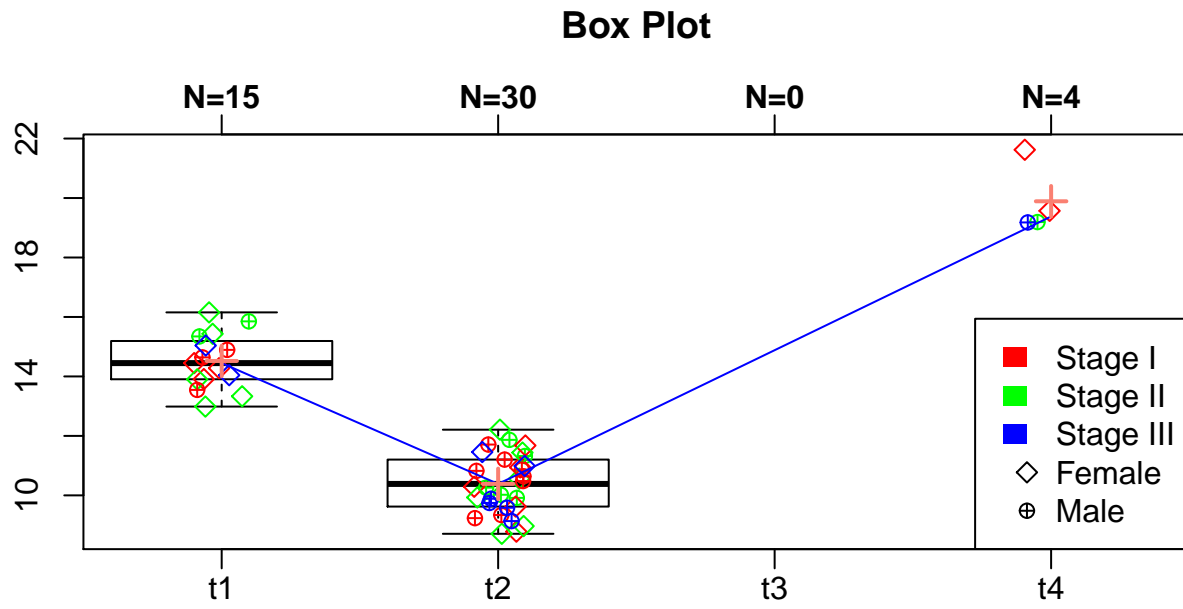


13.12 Use yet another grouping factor for plotting symbols in the stripchart

```
BoxPlot(example, y~time, trend="median", ylab="Y-Axis Label",
        sc.col=c("red", "blue", "green")[example$grp],
        sc.pch=c(5,10)[example$sex] )
```

Number of samples removed due to missing Y: 1

```
legend("bottomright", fill=c("red", "green", "blue", "white", "white"),
      legend=c("Stage I", "Stage II", "Stage III", "Female", "Male"),
      pch=c(-1, -1, -1, 5, 10), border=NA)
```

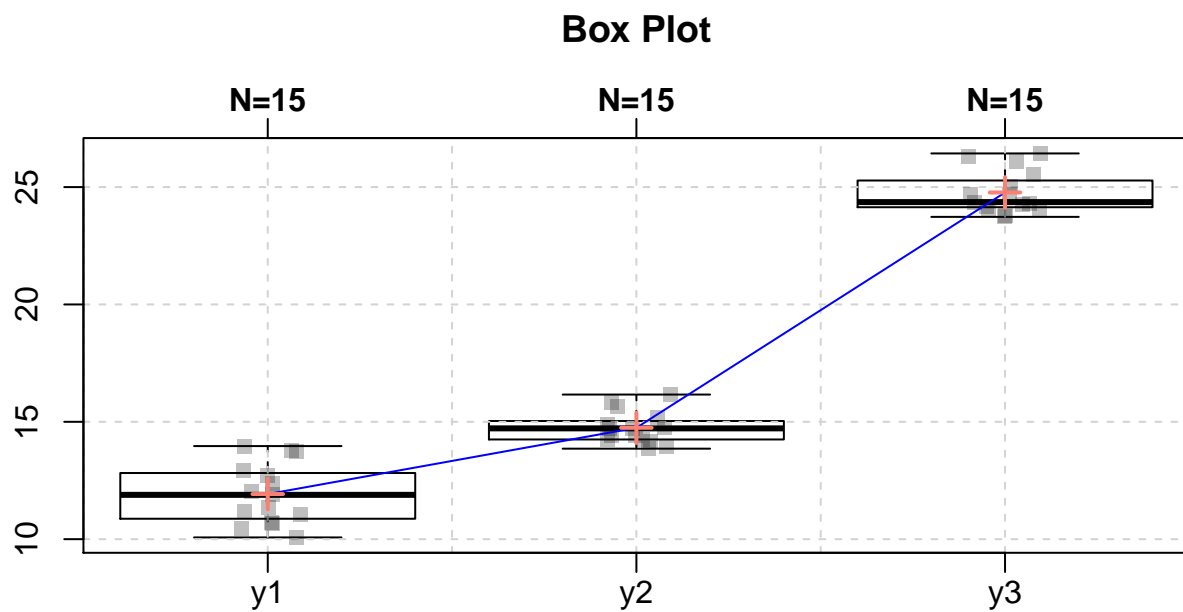


13.13 Generate new dataset with different structure

```
example2 <- data.frame(y1=12+rnorm(15), y2=15+rnorm(15), y3=25+rnorm(15))
```

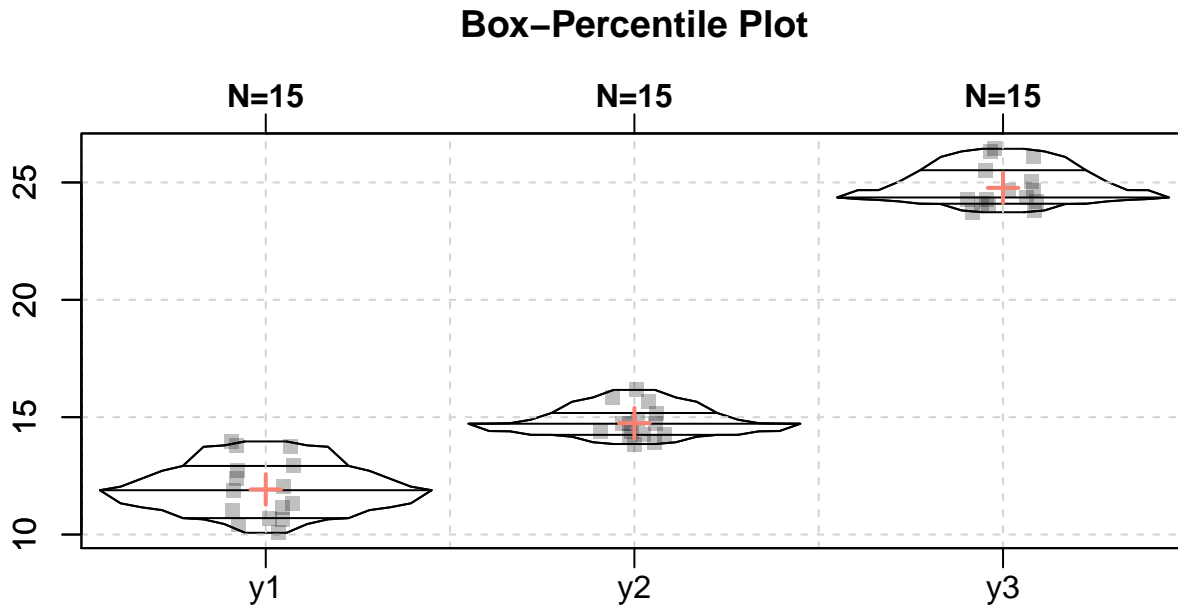
13.14 Boxplot with trend lines (mean) and grid added to the plot

```
BoxPlot(example2, var=c("y1", "y2", "y3"), Grid=TRUE, trend="mean")
```



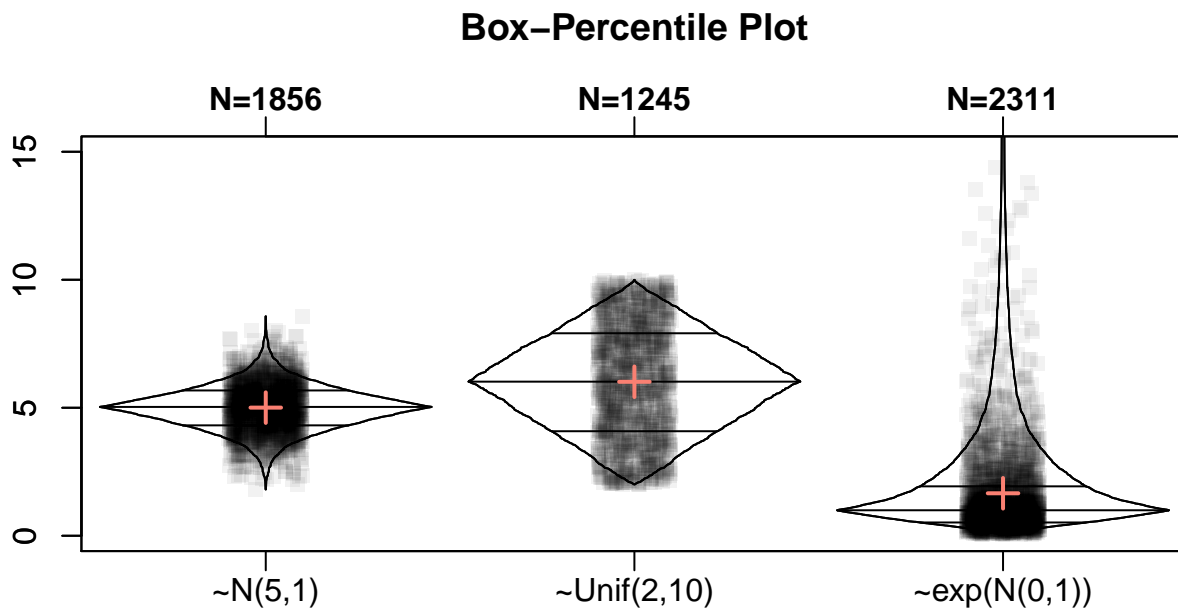
13.15 Now as box-percentile plot

```
BoxPlot(example2, var=c("y1", "y2", "y3"), box.type="bp", Grid=TRUE)
```



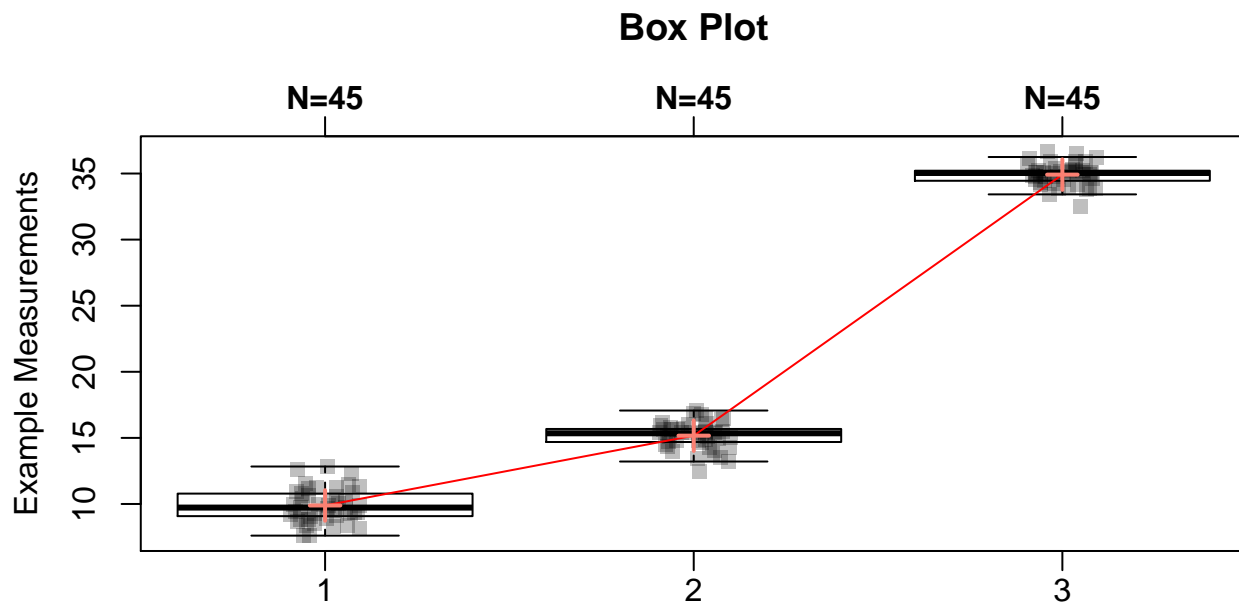
13.16 Use yet another way to specify the data

```
BoxPlot(rnorm(1856, 5), runif(1245, 2,10), exp(rnorm(2311)), sc.col=as.rgb("black", .05),
        box.type="bp", Xaxis=list(labels=c("~N(5,1)", "~Unif(2,10)", "~exp(N(0,1))")), ylim=c(0,15))
```



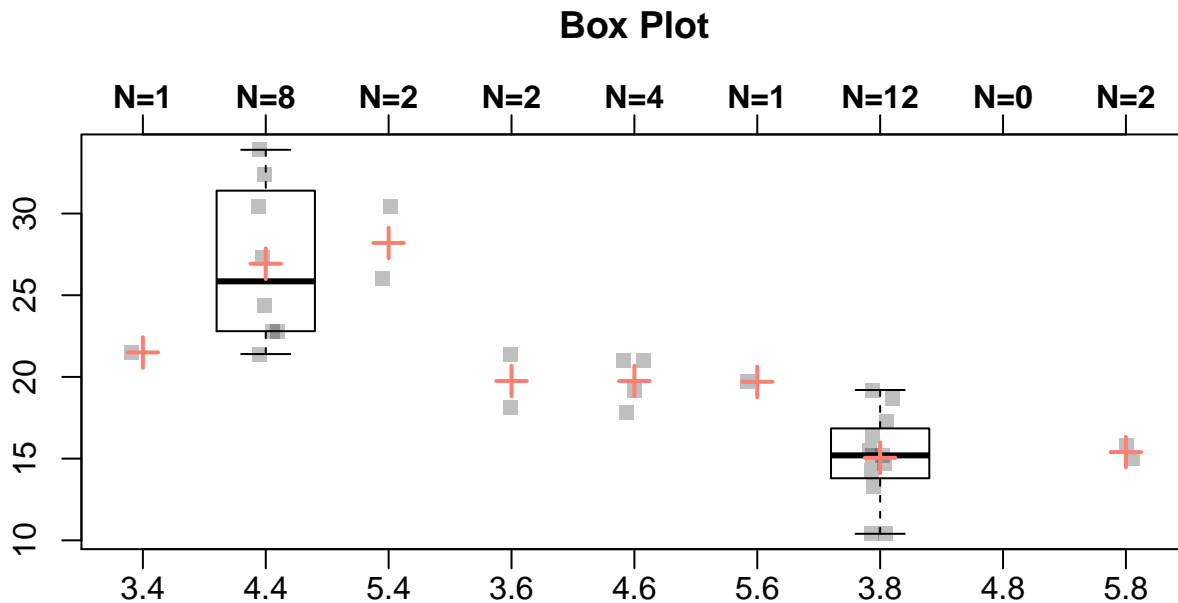
13.17 Specifying data as numeric matrix and using a trend-line connecting the means

```
mat <- matrix(c(rep(10,45), rep(15,45), rep(35,45))+rnorm(135), ncol=3)
BoxPlot(mat, trend="mean", trend.col="red", Ylabel=list(text="Example Measurements"))
```



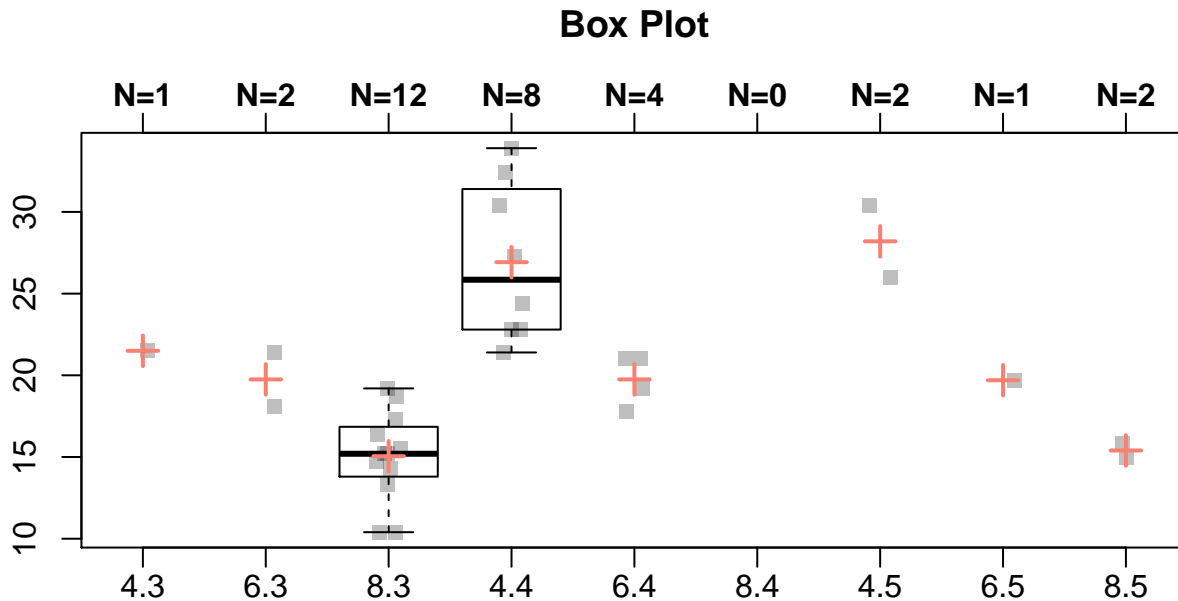
13.18 Multiple grouping factors can be specified via the formula interface which is exemplified using the mtcars dataset, of interest is miles per gallon (mpg) depending on number of gears and on the number of cylinders

```
data(mtcars)
BoxPlot(mtcars, mpg~gear:cyl)
```



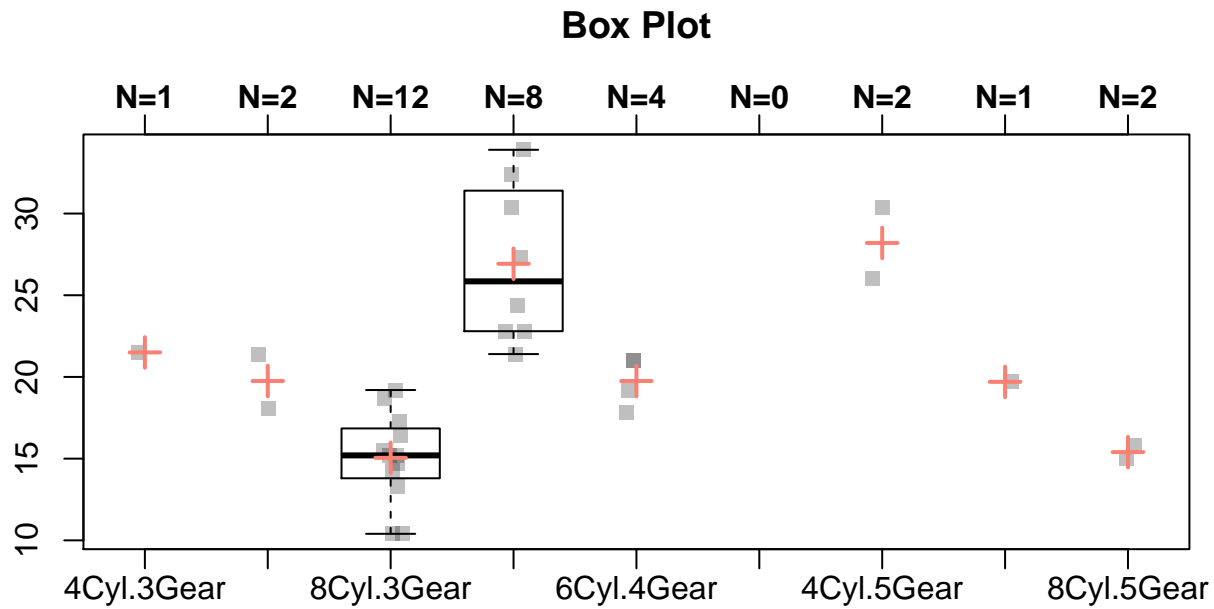
13.19 Now 'cyl' is explicitly nested within 'gear' which changes the ordering of combined grouping factors (which is identical to using formula 'mpg~cyl:gear').

```
BoxPlot(mtcars, mpg~cyl %in% gear)
```



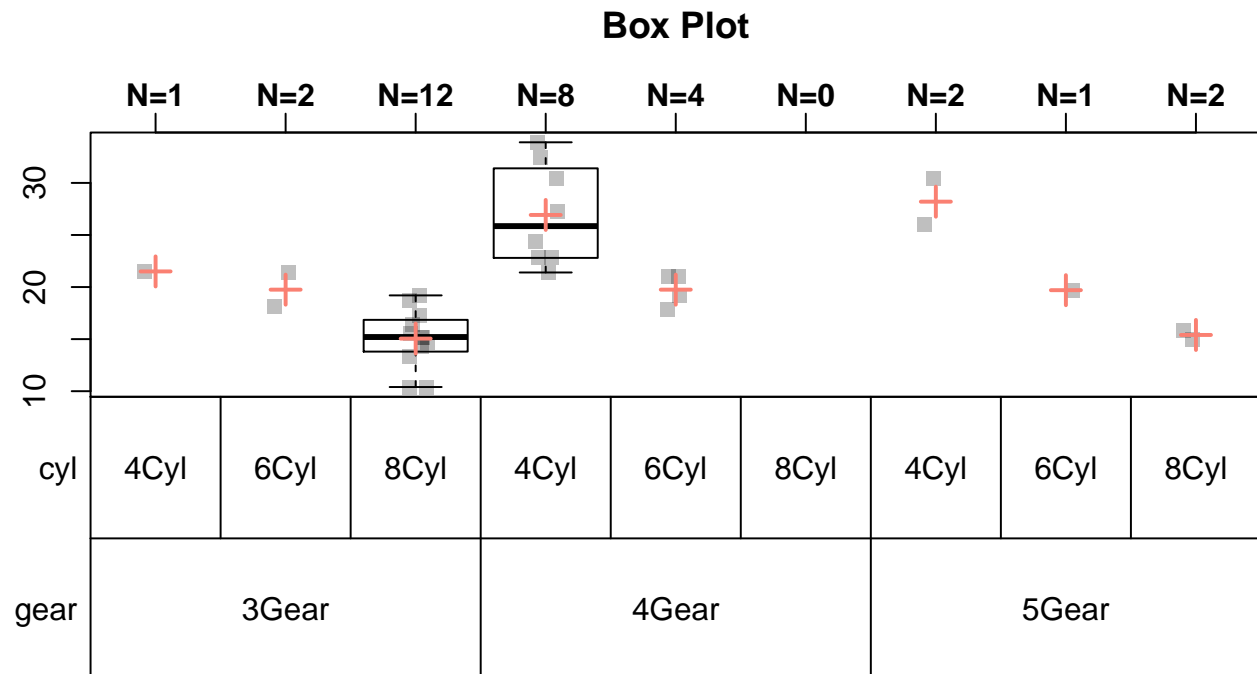
13.20 More meaningful group-labels are best specified using custom factor-level names (increase width of the plot window)

```
dat <- mtcars
dat$cyl <- factor(dat$cyl, levels=c(4,6,8), labels=c("4Cyl", "6Cyl", "8Cyl"))
dat$gear <- factor(dat$gear, levels=c(3,4,5), labels=c("3Gear", "4Gear", "5Gear"))
BoxPlot(dat, mpg~cyl %in% gear)
```



13.21 One can use a table as Xaxis label representing the factor-level combination defining sub-classes

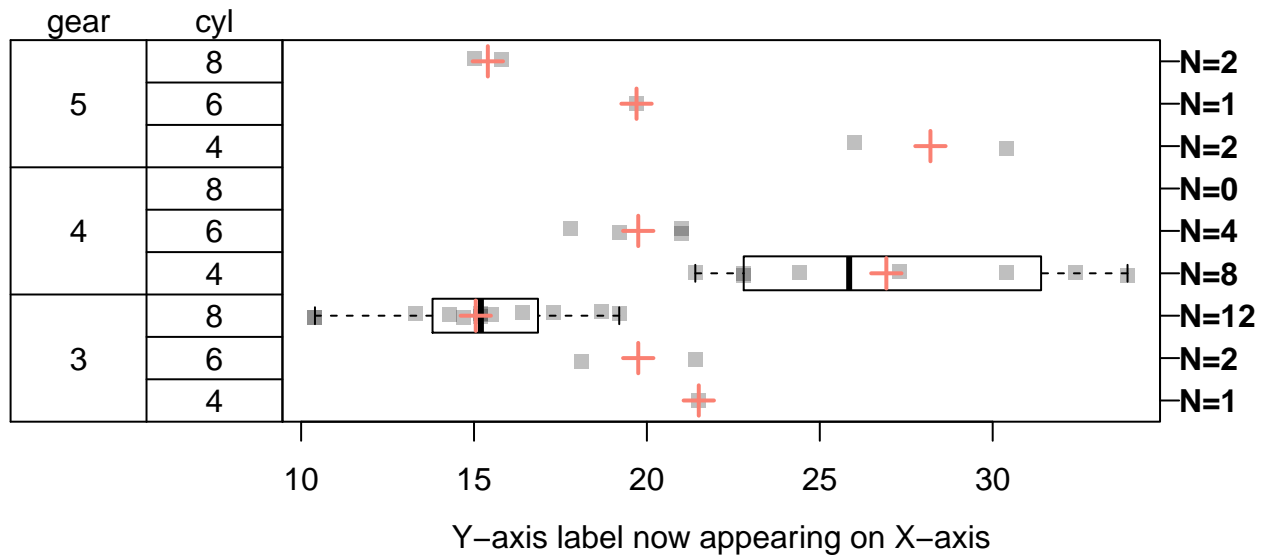
```
BoxPlot(dat, mpg~cyl:gear, XaxisTab=list(),mar=c(8,3,5,1))
```



13.22 With the original factor levels and as horizontal plot

```
BoxPlot(mtcars, mpg~cyl:gear, XaxisTab=list(), mar=c(5,8,5,4),
        horizontal=TRUE, Ylabel=list(text="Y-axis label now appearing on X-axis"))
```

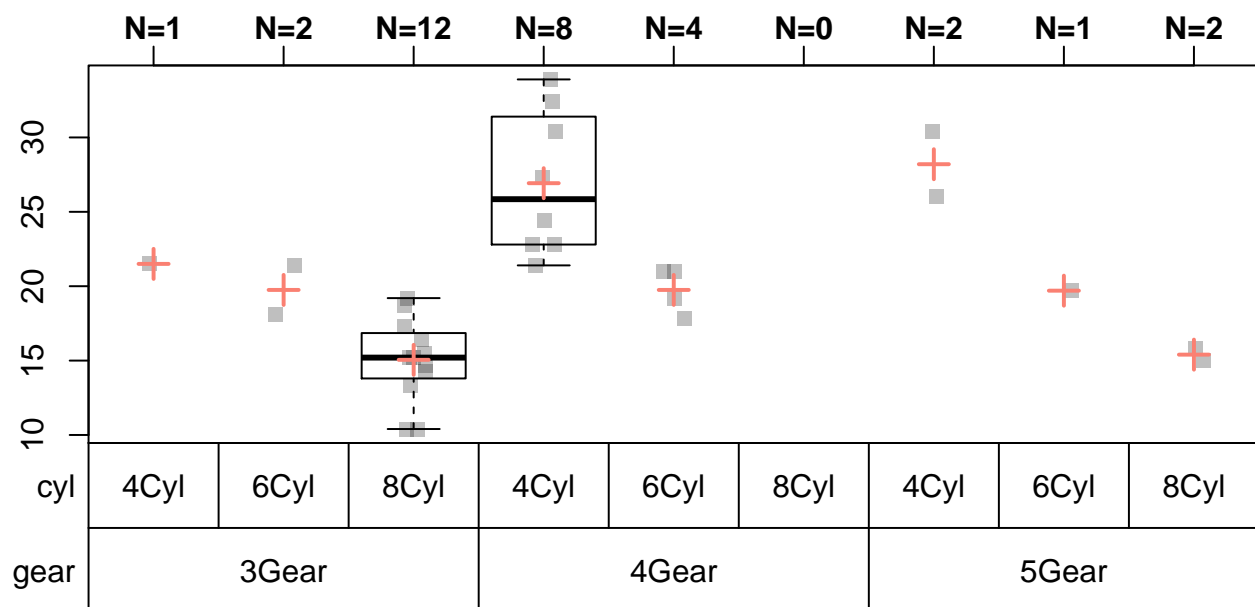
Box Plot



13.23 Using smaller bottom margin will result in smaller table height

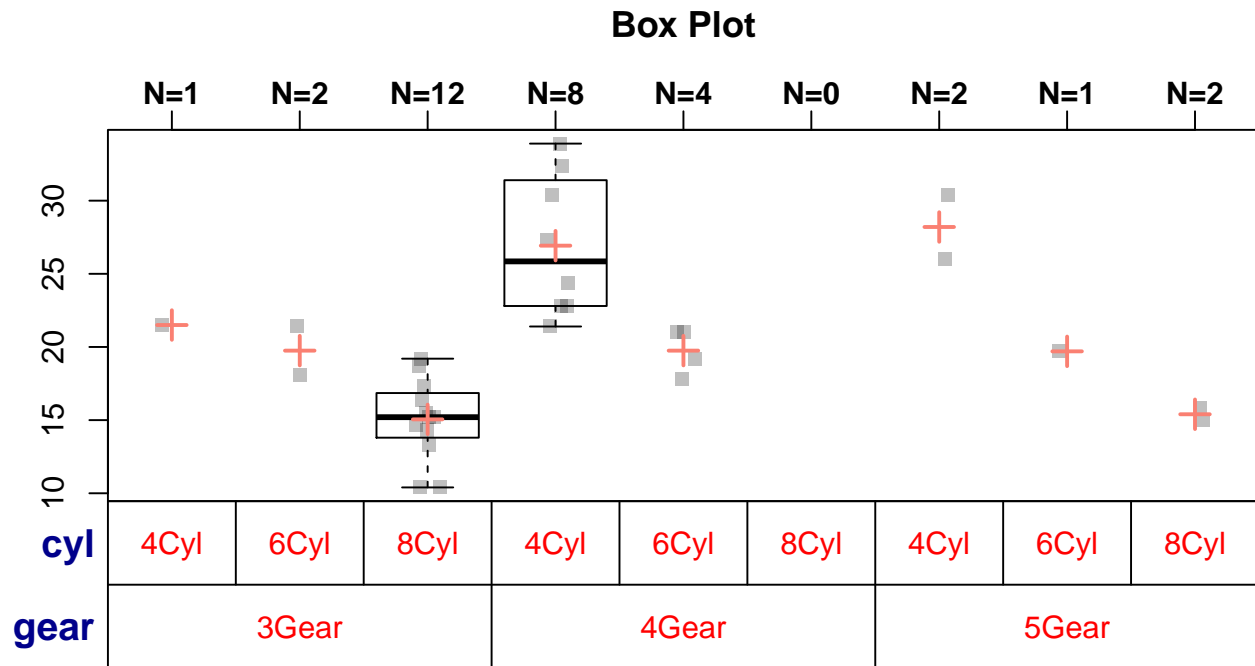
```
BoxPlot(dat, mpg~cyl:gear, XaxisTab=list(font=2, col="darkblue", cex=1.25), mar=c(5,3,5,1))
```

Box Plot



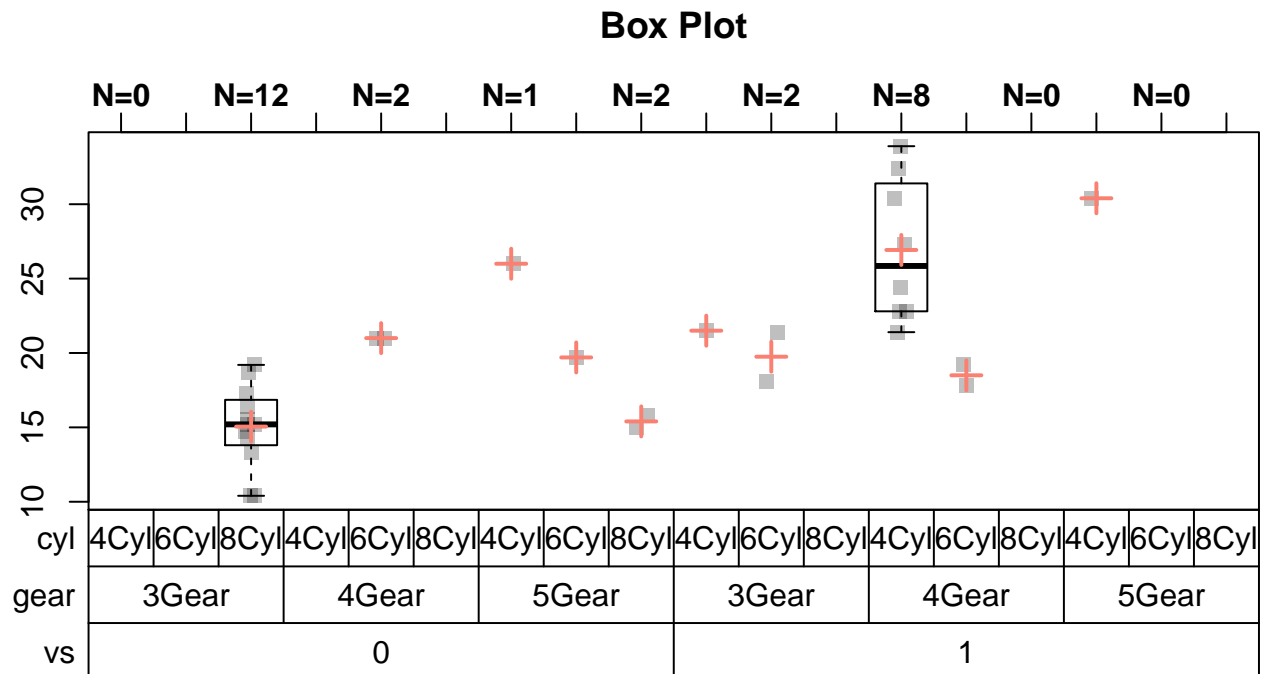
13.24 One can use different font-settings for rownames and cells of the table

```
BoxPlot(dat, mpg~cyl:gear, XaxisTab=list(Label=list(font=2, col="darkblue", cex=1.25),
      Text=list(col="red")), mar=c(5,3,5,1))
```



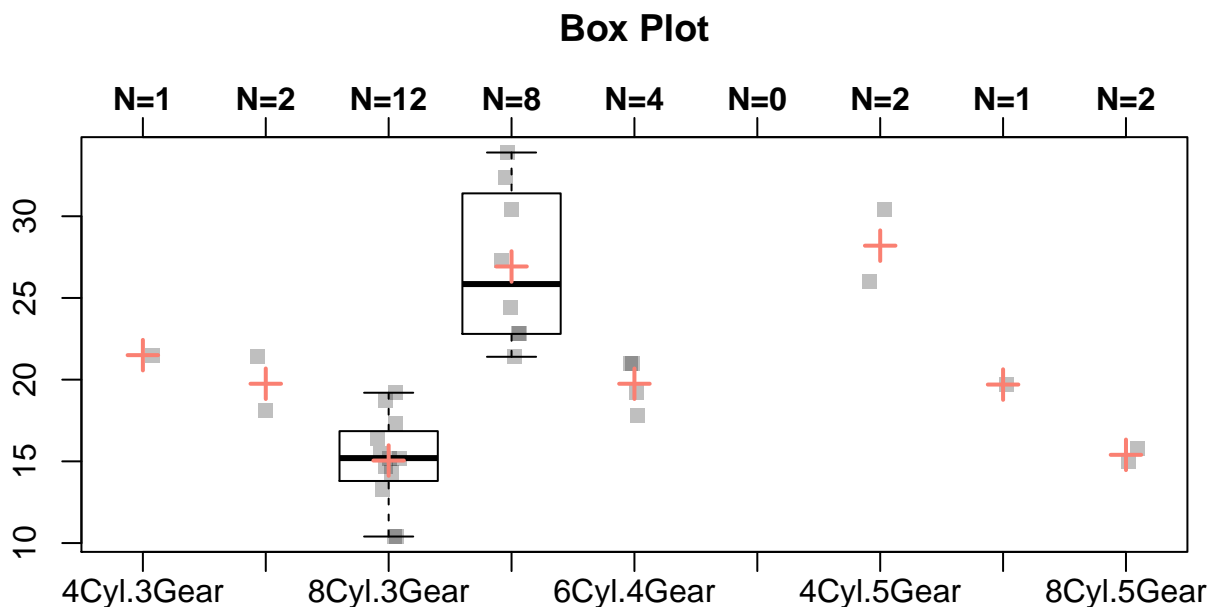
13.25 Use more crossed factors

```
BoxPlot(dat, mpg~cyl:gear:vs, XaxisTab=list(), mar=c(5,3,5,1))
```



13.26 Alternatively one can use the 'Xaxis' argument, but the ordering of these labels is not checked which is not important for automatically generated group-labels as shown in the previous example

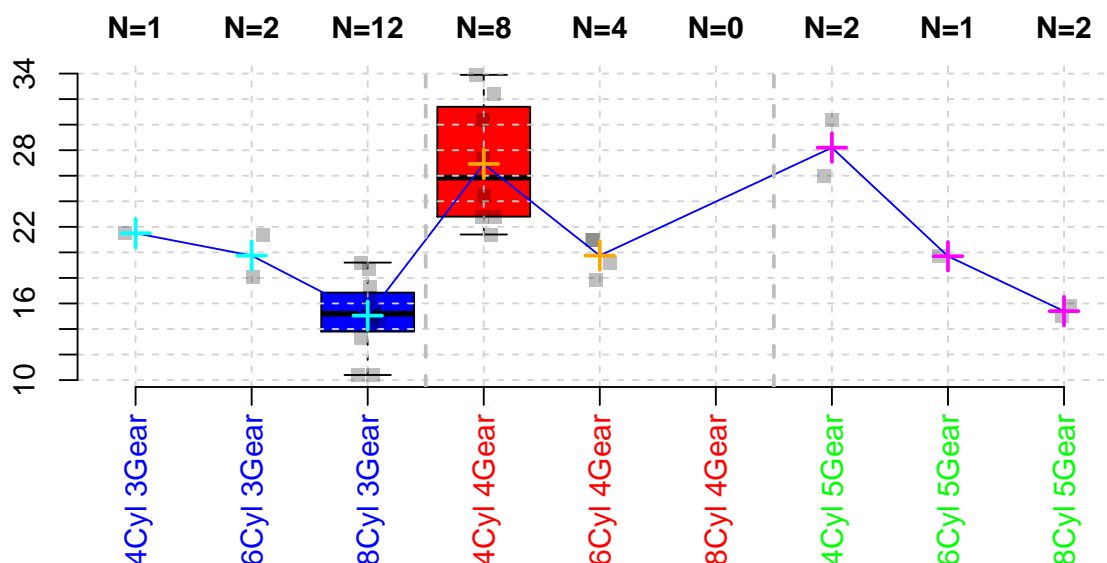
```
BoxPlot(mtcars, mpg~cyl %in% gear,
        Xaxis=list(labels=paste(rep(c("4Cyl", "6Cyl", "8Cyl"),3),
                                c(rep("3Gear",3), rep("4Gear",3), rep("5Gear",3)), sep="."))))
```



13.27 The same plot with some fancy options

```
BoxPlot(dat, mpg~cyl %in% gear, Title=list(main="Miles per Gallon by Number of Gears",
      col.main="Green", cex.main=2.5), vline=c(3.5, 6.5), vl.lty=2, vl.col="gray", vl.lwd=2,
      Xaxis=list(labels=NA, at=1:9, tick=TRUE), col=c(rep("blue", 3), rep("red", 3), rep("green", 3)),
      Xaxis2=list(tick=FALSE), Yaxis=list(at=seq(10,34,2)), Grid=list(x=1:9, y=seq(10,34,2)),
      Xlabel=list(text=paste(rep(c("4Cyl", "6Cyl", "8Cyl"),3), c(rep("3Gear",3), rep("4Gear",3), rep("5Gear",3)),
      at=1:9, las=2, adj=1, line=0.75, col=c(rep("blue", 3), rep("red", 3), rep("green", 3)),
      mean.col=c(rep("cyan", 3), rep("orange", 3), rep("magenta", 3)), Box=FALSE, trend="mean", mar=c(3, 7, 4, 4))
```

Miles per Gallon by Number of Gears

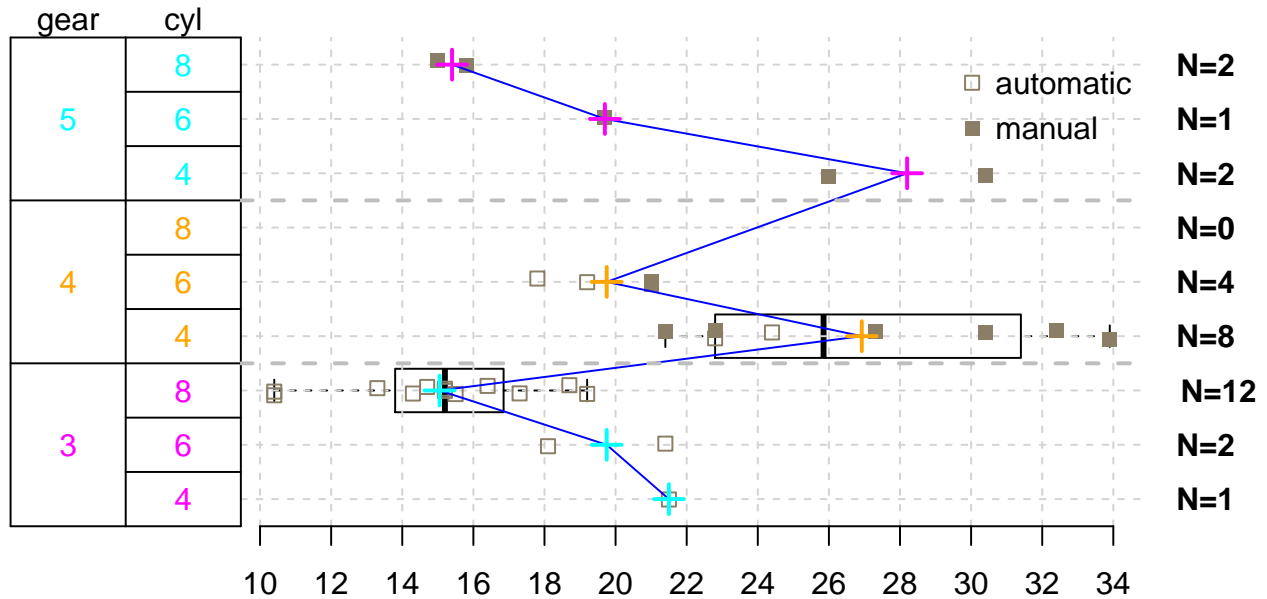


13.28 Horizontal fancy plot

```
BoxPlot(mtcars, mpg~cyl %in% gear, Title=list(main="Miles per Gallon by Number of Gears", col.main="#84
      vline=c(3.5, 6.5), vl.lty=2, vl.col="gray", vl.lwd=2,
      Xaxis2=list(tick=FALSE, las=2, hadj=-.25), Yaxis=list(at=seq(10,34,2)), Grid=list(x=1:9, y=seq(
      mean.col=c(rep("cyan", 3), rep("orange", 3), rep("magenta", 3)), Box=FALSE, trend="mean",
      mar=c(3, 7, 4, 4), horizontal=TRUE, sc.pch=c(0, 15)[dat$am+1], sc.col="wheat4",
      XaxisTab=list(Text=list(col=c(rep("cyan", 3), rep("orange", 3), rep("magenta", 3)))) )

legend(x="topright", pch=c(0, 15), legend=c("automatic", "manual"), box.lty=0, col="wheat4")
```


Miles per Gallon by Number of Gears



14 Longitudinal analysis

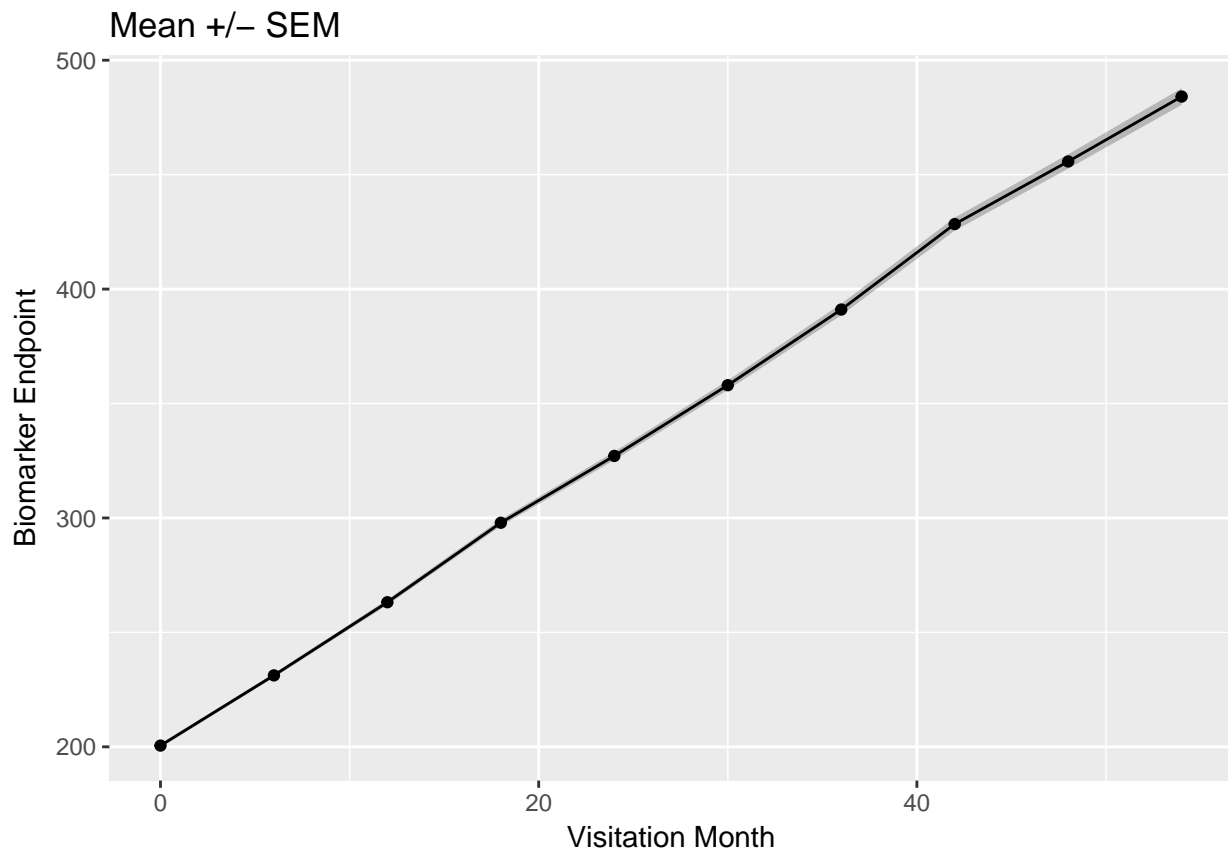
In the context of biomarker analysis, the `PlotLong` function can be used to plot the longitudinal measurement of a biomarker endpoint for one or more patient subpopulations. Here we'll use the packaged dataset `bmkr` (biomarker) which has columns for patient ID (`pid`), treatment (`trt`), gender (`sex`), visitation month (`vm`) and endpoint reading (`ep`)

14.1 Biomarker Endpoint Progression

14.1.1 Mean +/- SEM Timecourse

Here we plot the mean and standard error of the mean over time. We can see clearly that the mean biomarker endpoint increases throughout the study.

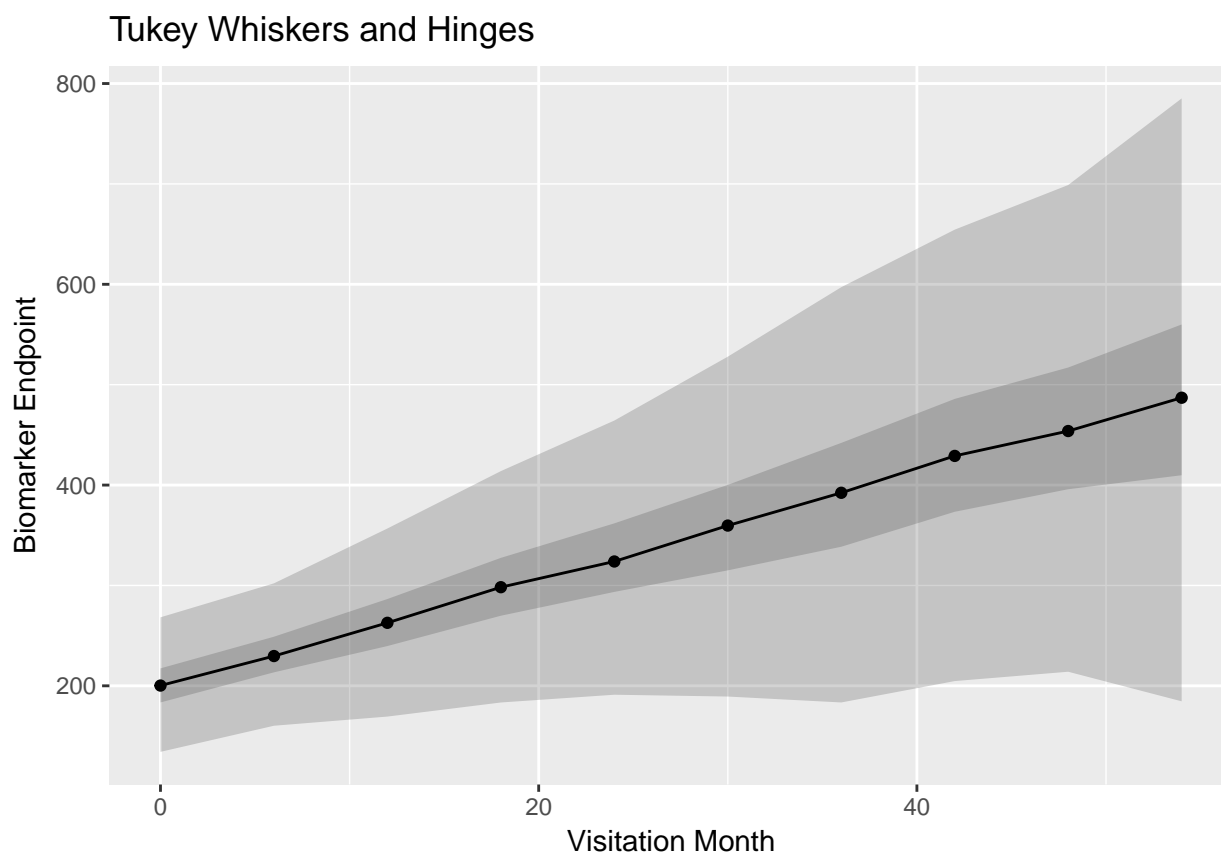
```
PlotLong(longbmkr, aes(x=vm, y=ep),
  xlab = 'Visitation Month',
  ylab = 'Biomarker Endpoint',
  labs.title = 'Mean +/- SEM')
```



14.1.2 Tukey Hinges and Whiskers

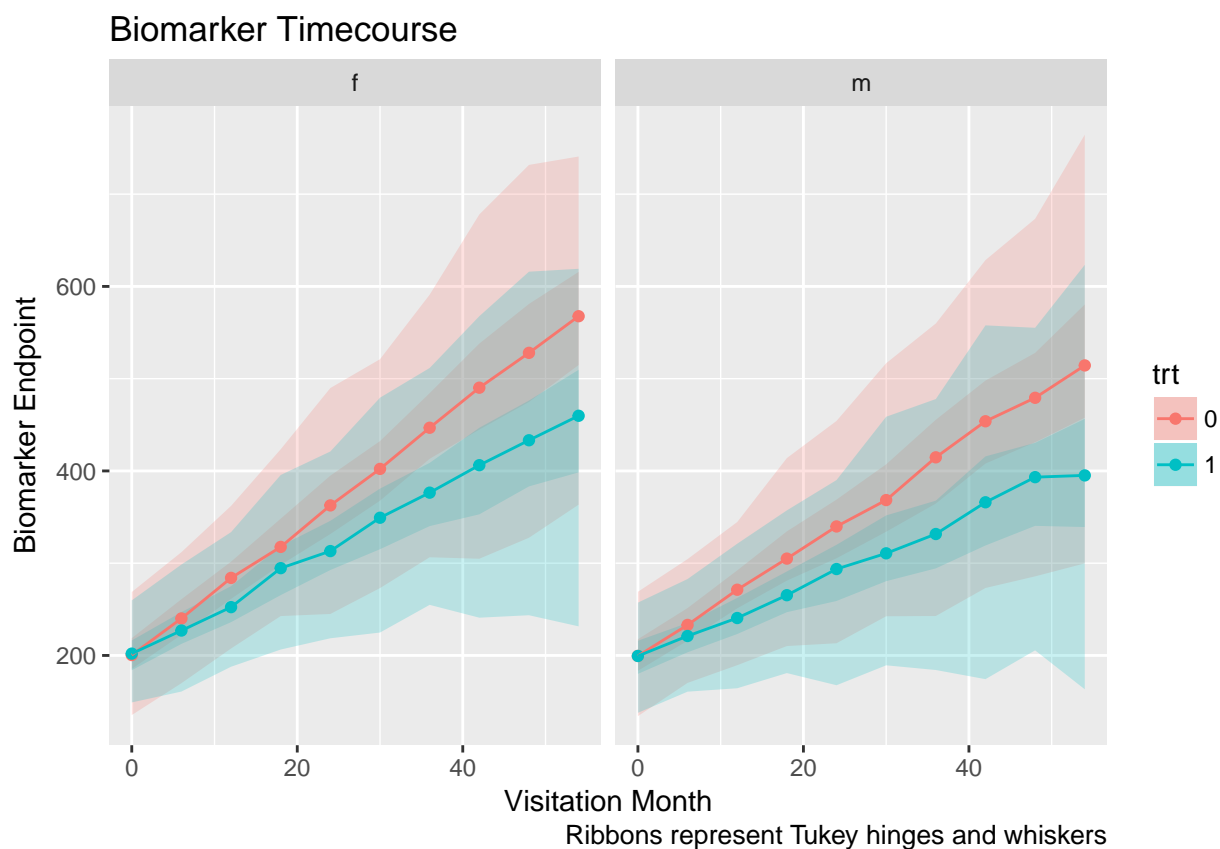
However, we may be more interested in the population distribution progression where we'd want to plot the Tukey boxplot hinges and whiskers over time. From this plot, we can see that although there is a slow rise in population mean, the patient response also becomes more distributed.

```
PlotLong(longbmkr, aes(x=vm, y=ep), fun.data = 'tukey',  
         xlab = 'Visitation Month',  
         ylab = 'Biomarker Endpoint',  
         labs.title = 'Tukey Whiskers and Hinges')
```



14.2 Plotting Subpopulations

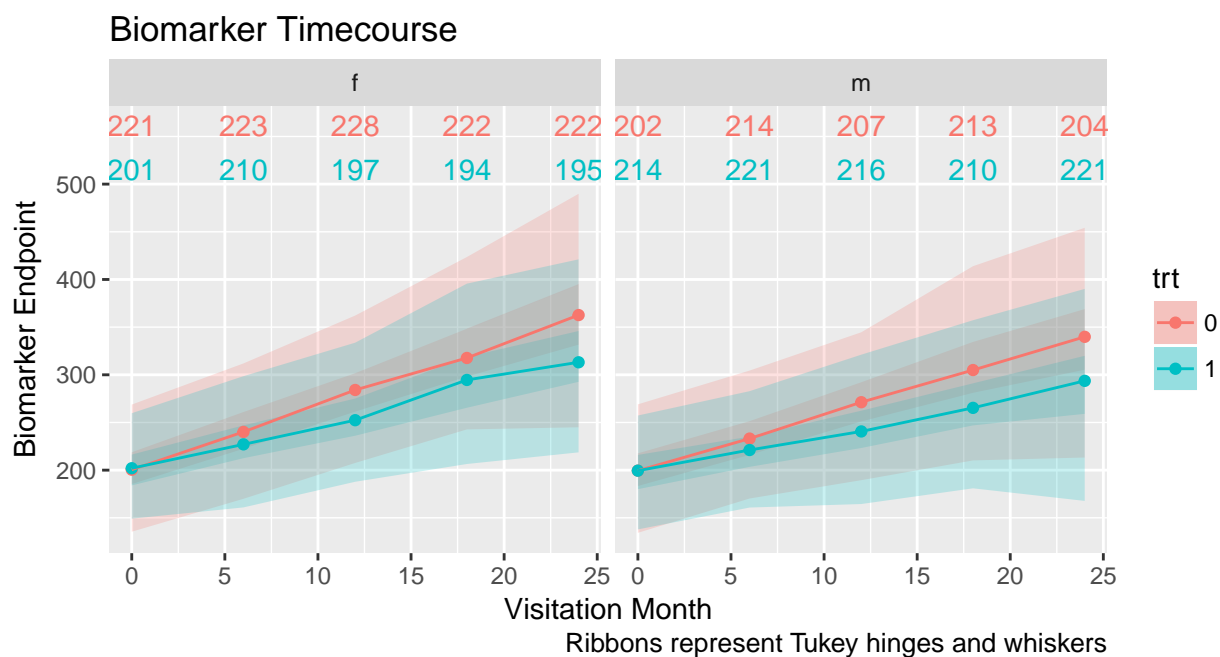
```
PlotLong(longbmkrr, aes(x=vm, y=ep, group=trt, color=trt, fill=trt),  
  fun.data = 'tukey', facet.fun = . ~ sex,  
  xlab = 'Visitation Month',  
  ylab = 'Biomarker Endpoint',  
  labs.title = 'Biomarker Timecourse',  
  labs.caption = 'Ribbons represent Tukey hinges and whiskers')
```



14.3 Including sample counts

14.3.1 Sample counts as table above plot

```
library(dplyr)
PlotLong(longbmkr %>% filter(vm <= 24),
  aes(x=vm, y=ep, group=trt, color=trt, fill=trt),
  fun.data = 'tukey', facet.fun = . ~ sex,
  show.counts = 'table',
  xlab = 'Visitation Month',
  ylab = 'Biomarker Endpoint',
  labs.title = 'Biomarker Timecourse',
  labs.caption = 'Ribbons represent Tukey hinges and whiskers')
```



14.4 Plotting Deviations as Errorbars

```
PlotLong(longbmr %>% filter(vm <= 24),
  aes(x=vm, y=ep, group=trt, color=trt, fill=trt),
  fun.data = 'tukey', facet.fun = . ~ sex,
  show.counts = 'table',
  plot.style = 'errorbars',
  xlab = 'Visitation Month',
  ylab = 'Biomarker Endpoint',
  labs.title = 'Biomarker Timecourse',
  labs.caption = 'Ribbons represent Tukey hinges and whiskers')
```

