gClinBiomarker: example use cases

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Contents

1 Loading packages and data

```
library(knitr)
library(devtools)
```

```
## Warning: package 'devtools' was built under R version 3.3.2
```

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

```
## Warning: package 'survival' was built under R version 3.3.2
```

```
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	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%)

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	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)
)
```

	All(CTRL)	BEP(CTRL)	pvalue(CTRL)	All(TRT)	BEP(TRT)	pvalue(TRT)
Age						
N	182	81	0.5	368	176	0.69
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	182	81	0.88	368	176	0.75
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%)	

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)
	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	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	550	257
NA's	0	0
F	273 (49.64%)	129 (50.19%)
M	277 (50.36%)	128 (49.81%)

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)
```

Distribution of KRAS.exprs

N= 461

Mean: 5.97
SD: 1.99
Median: 6.14
Range: (0.51 – 13.22)

KRAS.exprs (log2 scale)
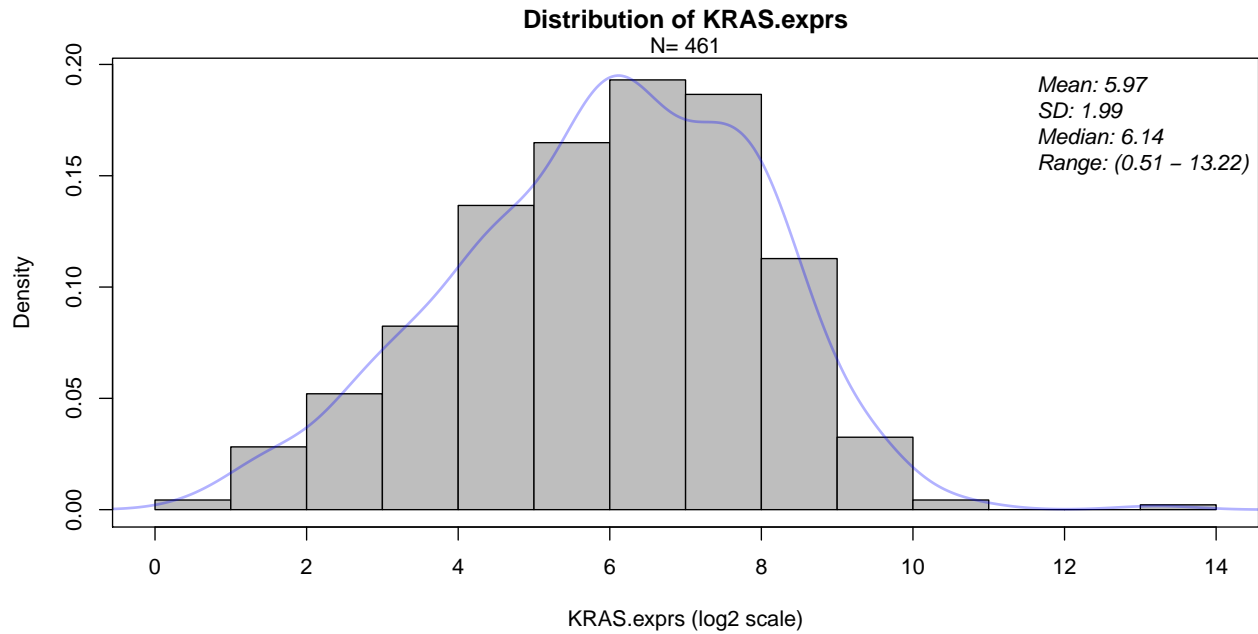
4.2 No biomarker variable. Two numeric clinical variables. Log transformation for one varible.

```
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))
```

Distribution of Weight

N= 550

Mean: 6.04
SD: 0.32
Median: 6
Range: (5.13 – 7.3)

Weight (log2 scale)

Distribution of Age

N= 550

Mean: 53.53
SD: 10.56
Median: 53
Range: (27 – 89)

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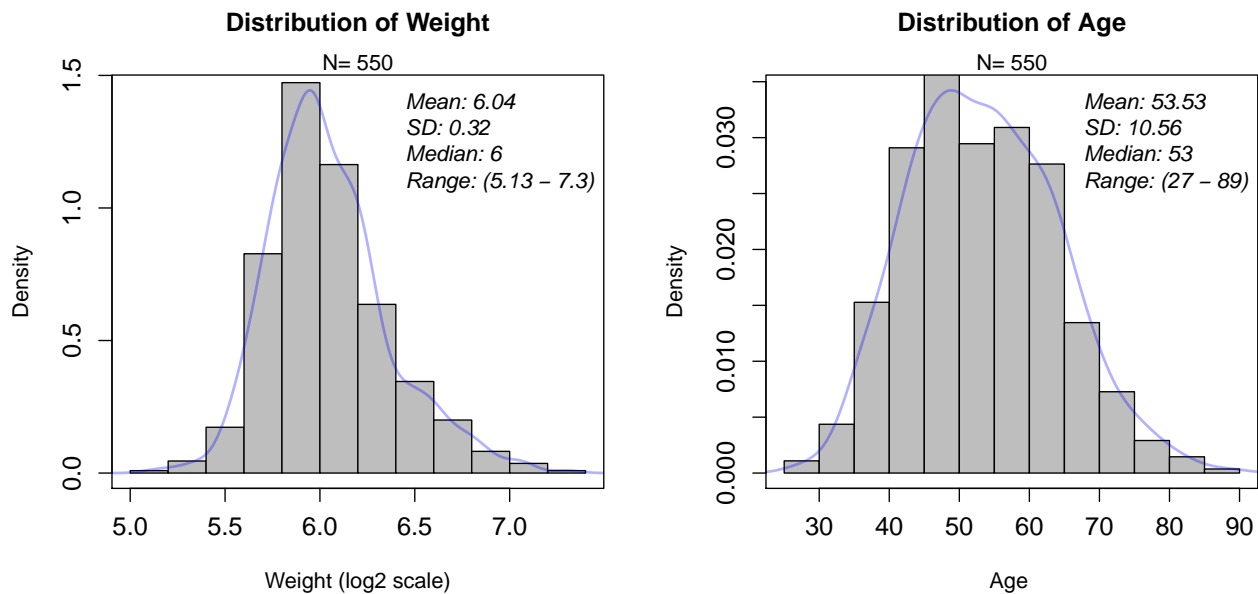
4.3 Numeric biomarker variable. Two clinical categorical variables. Log transformation for numeric variable.

```
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)
```
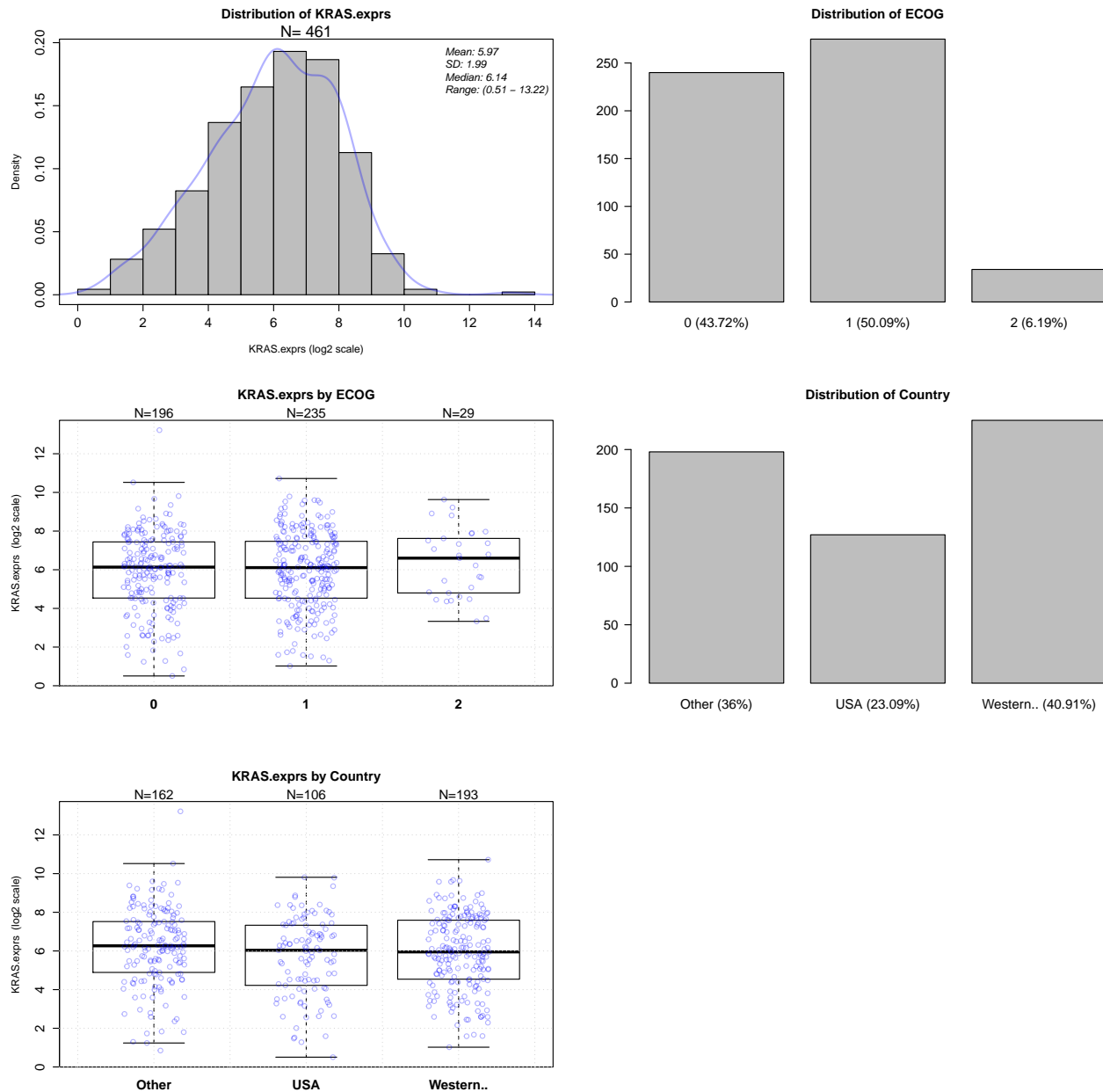

4.4 Numeric biomarker variable. Two clinical variables: one is categorocal, second is numeric. Log transformation for biomarker (numeric) variable.

```
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)
```
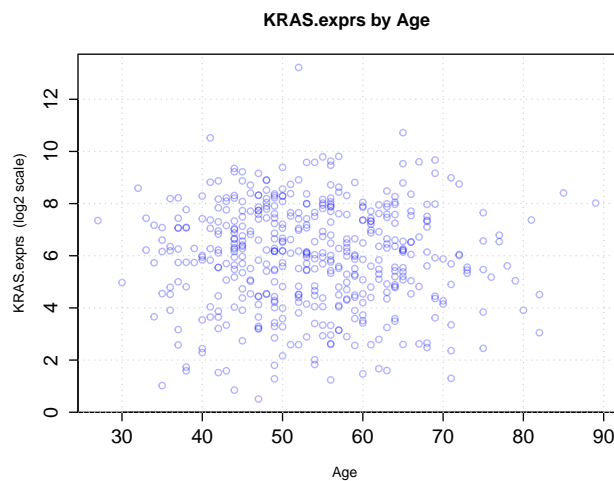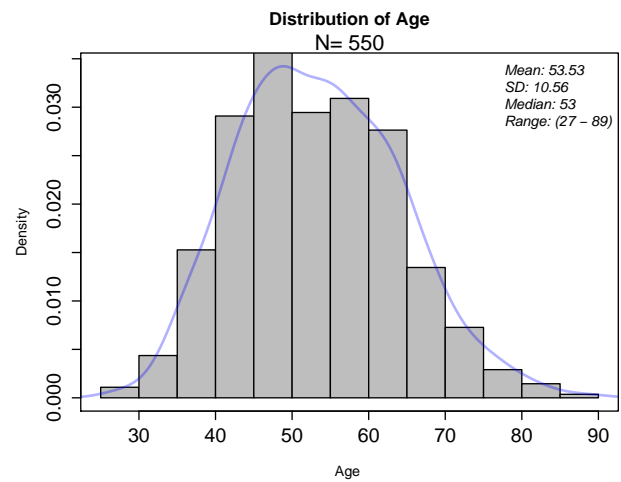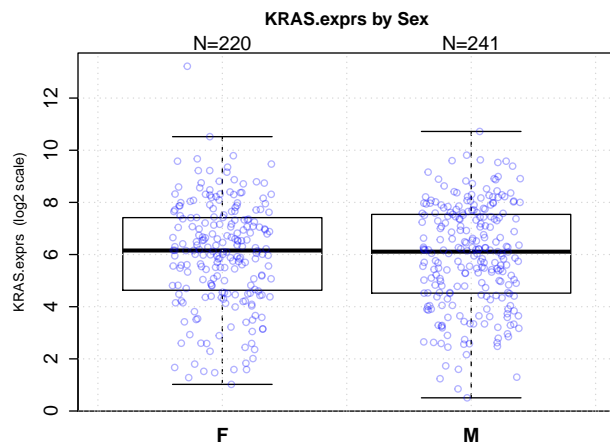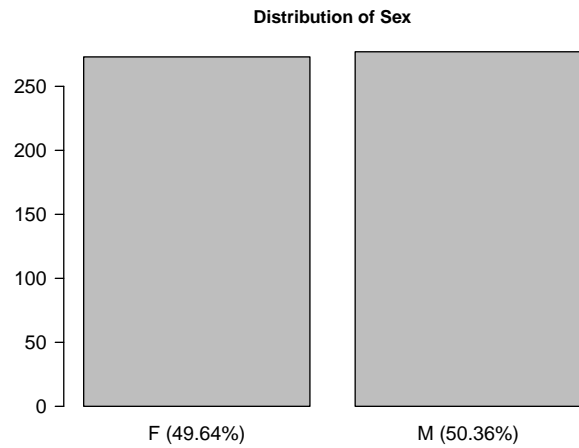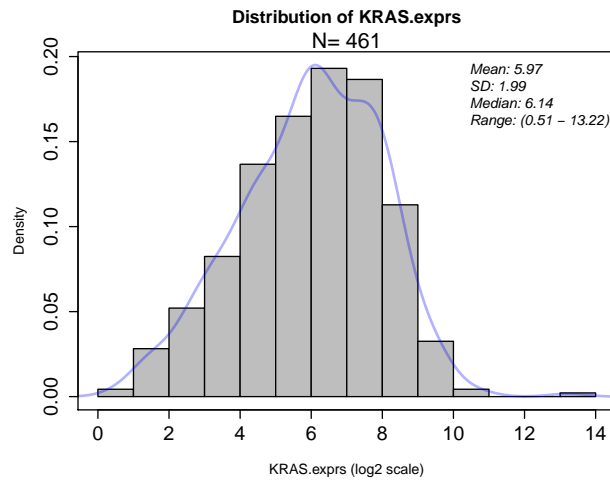
4.5 Categorical biomarker variable. Categorical clinical variable.

```
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 Categorial 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 Categorial 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)
```

Distribution of Country

Distribution of KRAS.mutant by Country

Distribution of Age

Age by KRAS.mutant

4.8 Categorial 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 Categorial 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)
```
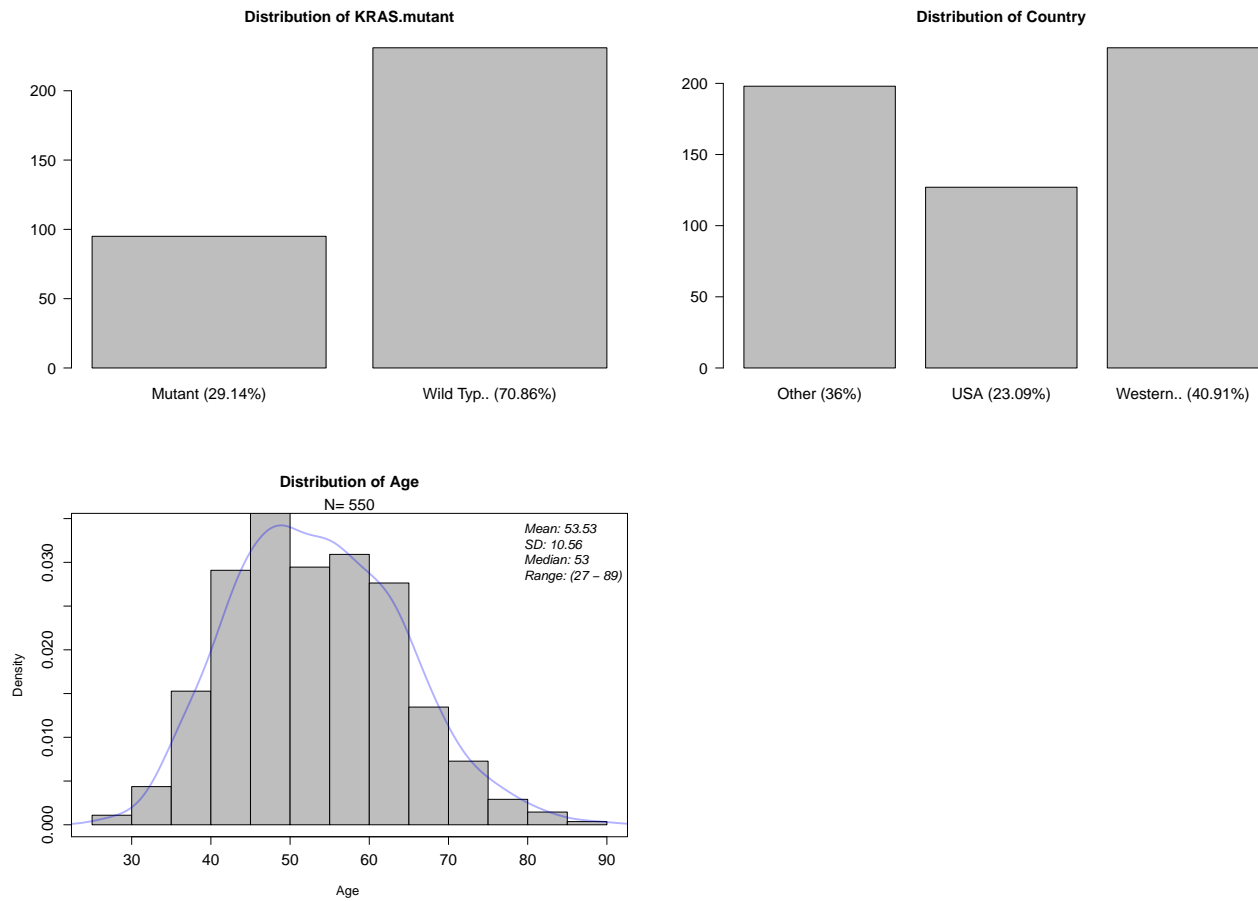
Distribution of KRAS.mutant

Distribution of Country

Distribution of Age
N= 550

Mean: 53.53
SD: 10.56
Median: 53
Range: (27 – 89)

4.10 Categorial 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)
```
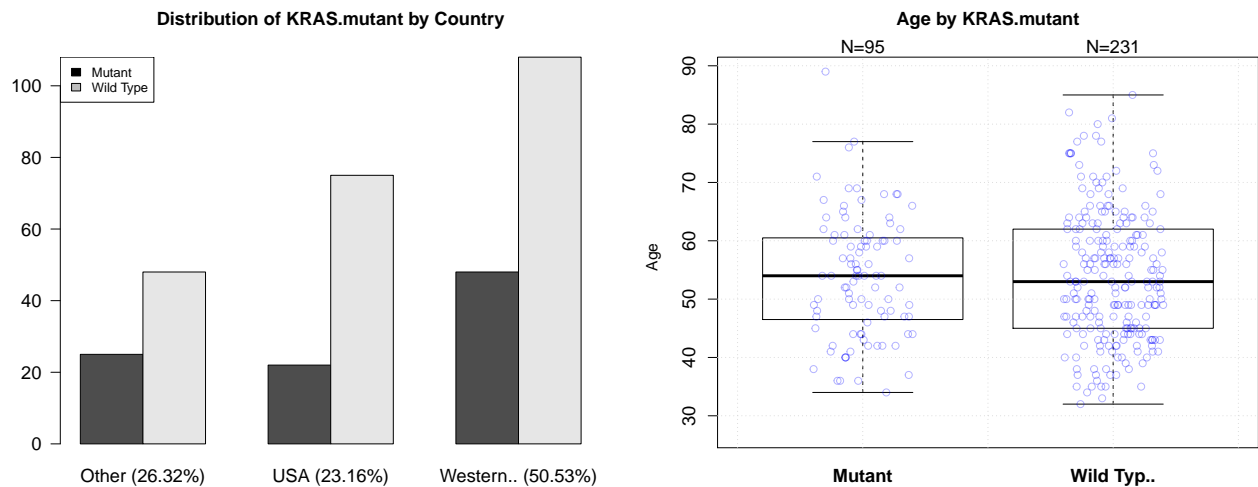

Distribution of KRAS.mutant by Country

Age by KRAS.mutant

4.11 Categorial 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)
```
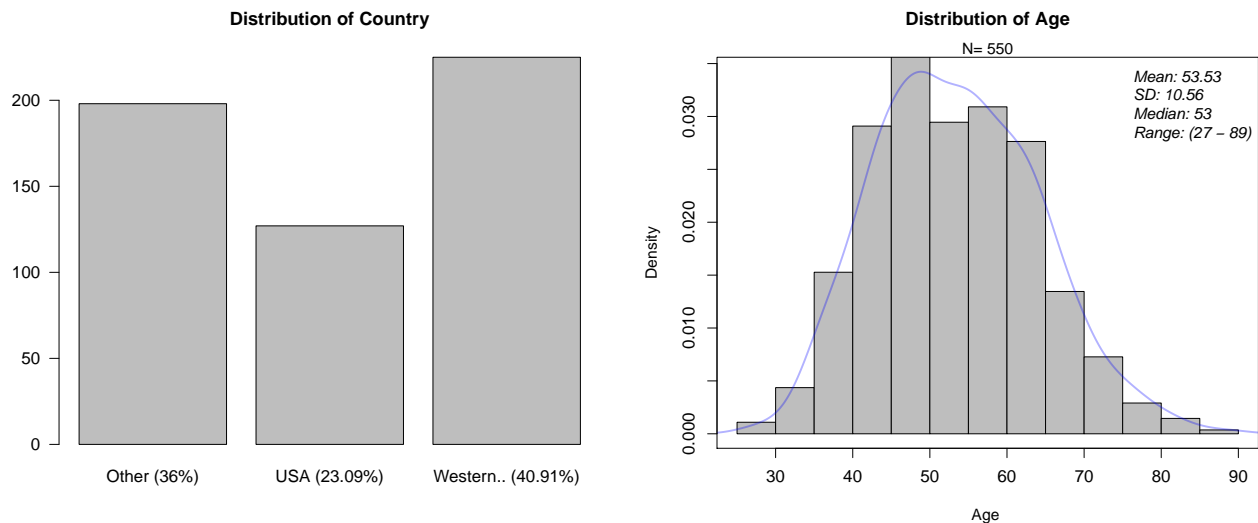

Categorial biomarker variable. Categorical and numeric clinical variables. No log transformation. Plot only biomarker variable.

```
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)
```
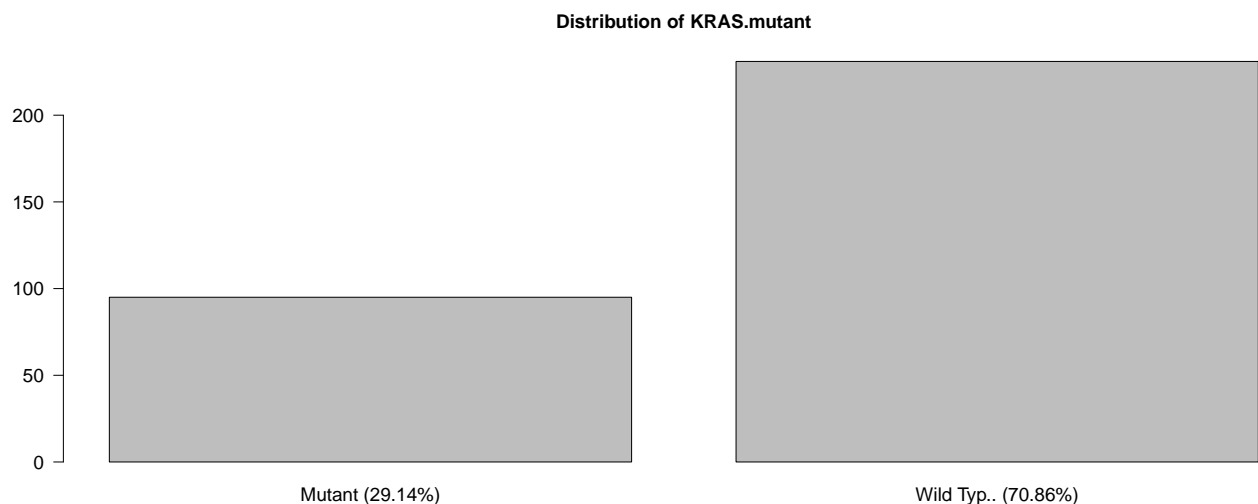
5   PlotRspBar(): Compare response outcome across different population

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

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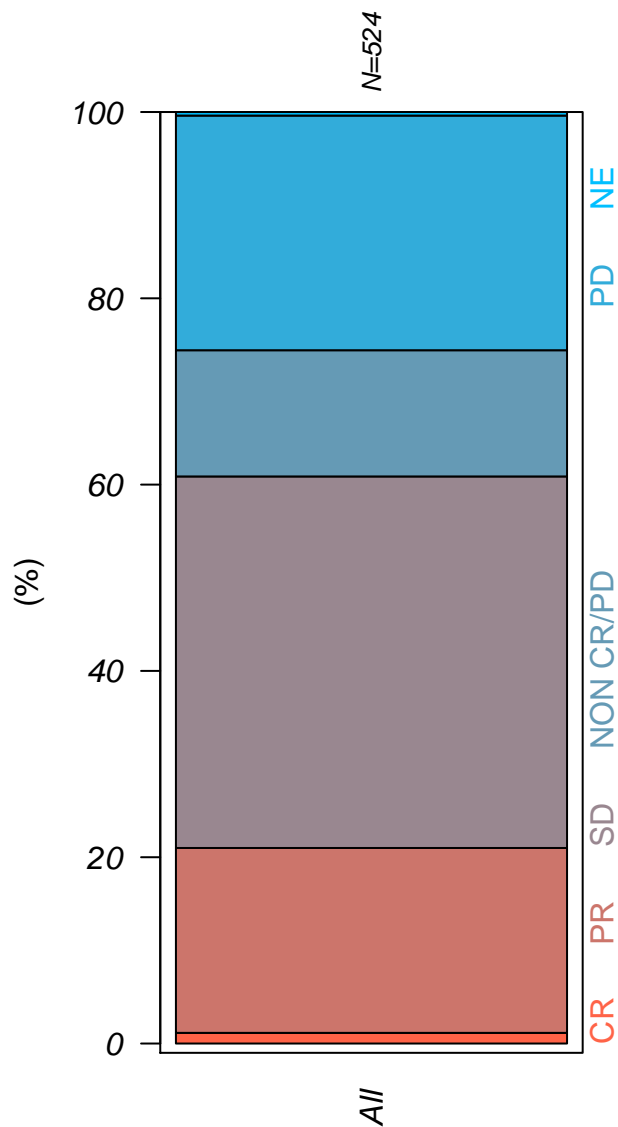
5.2 Plot response of one population, binarize outcome (classify classes to responder vs non responder)

```
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
```

Association of response rate
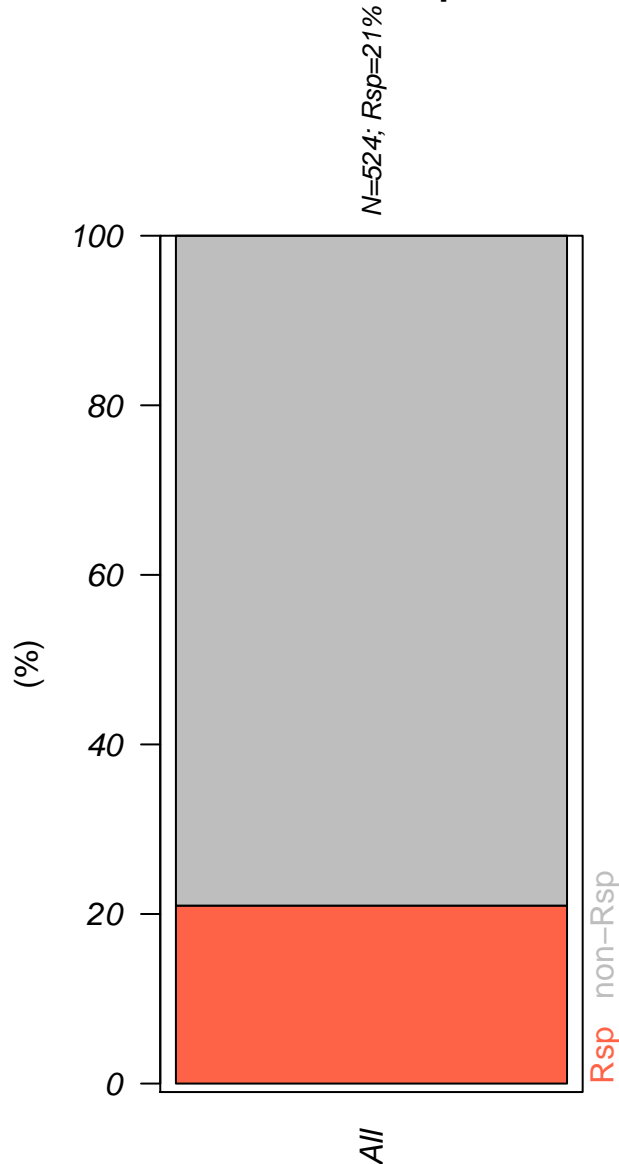
5.3 Change color

```
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
```

Association of response rate
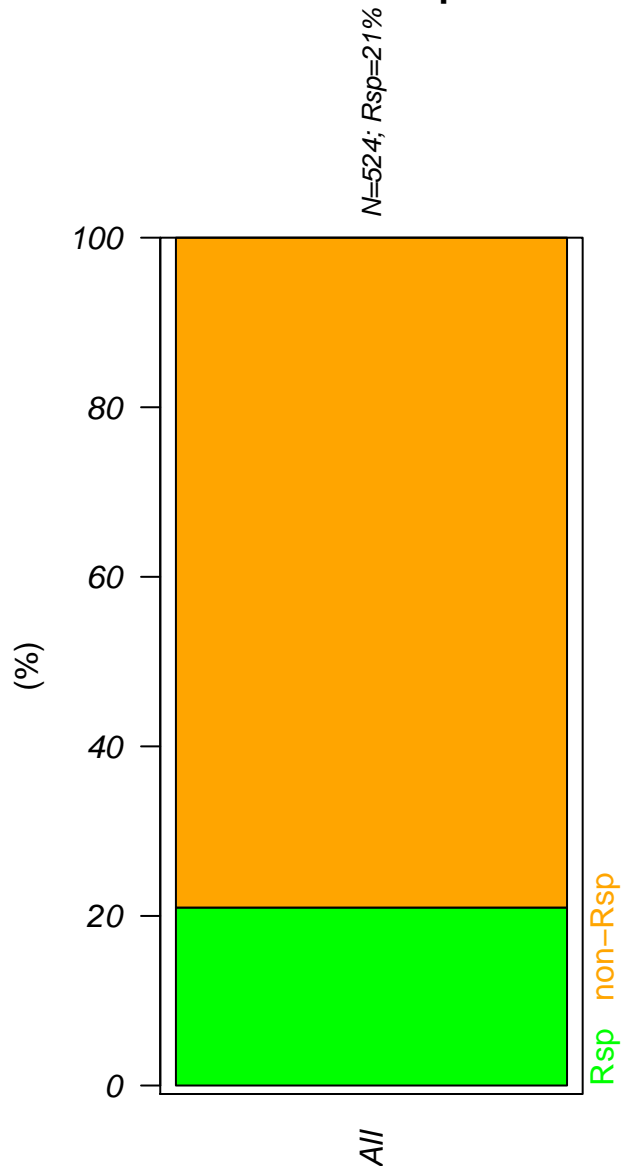
5.4 Plot horizontally

```
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
```

Rsp

non-Rsp

All

N=524; Rsp=21%

0   20   40   60   80   100

(%)
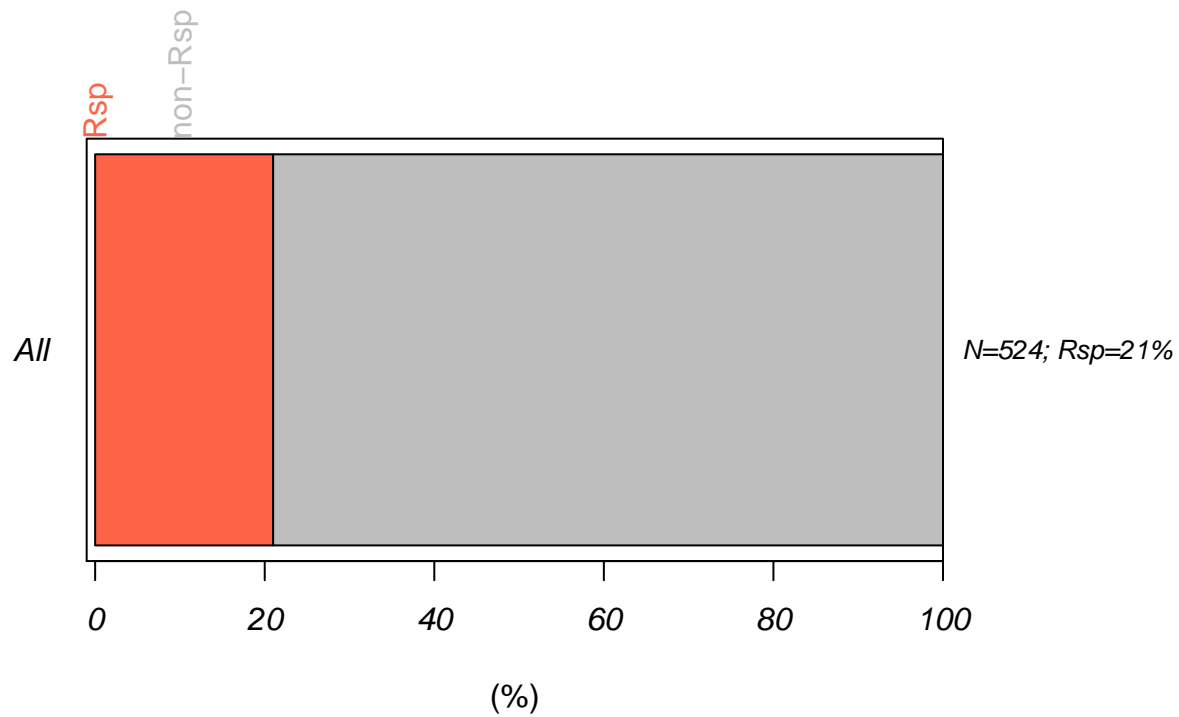
5.5 By arm

```
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
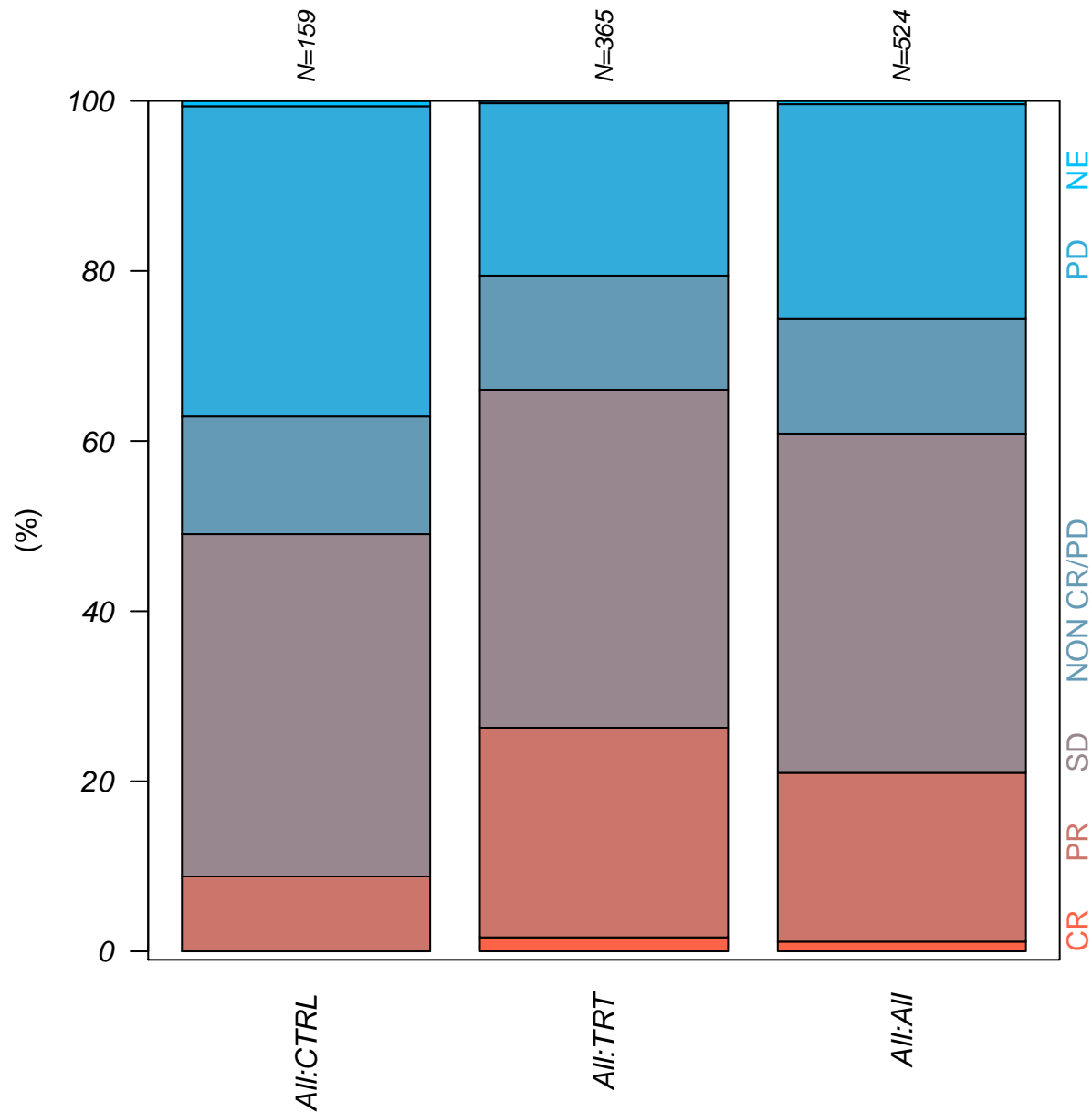

```
PlotRspBar (input, outcome.var="Response",
            binary=TRUE,
            rsp.response = c("CR","PR"),
            rsp.nonresponse = c("SD", "PD","NON CR/PD","NE",NA),
            trt="Arm")
```

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

Association of response rate
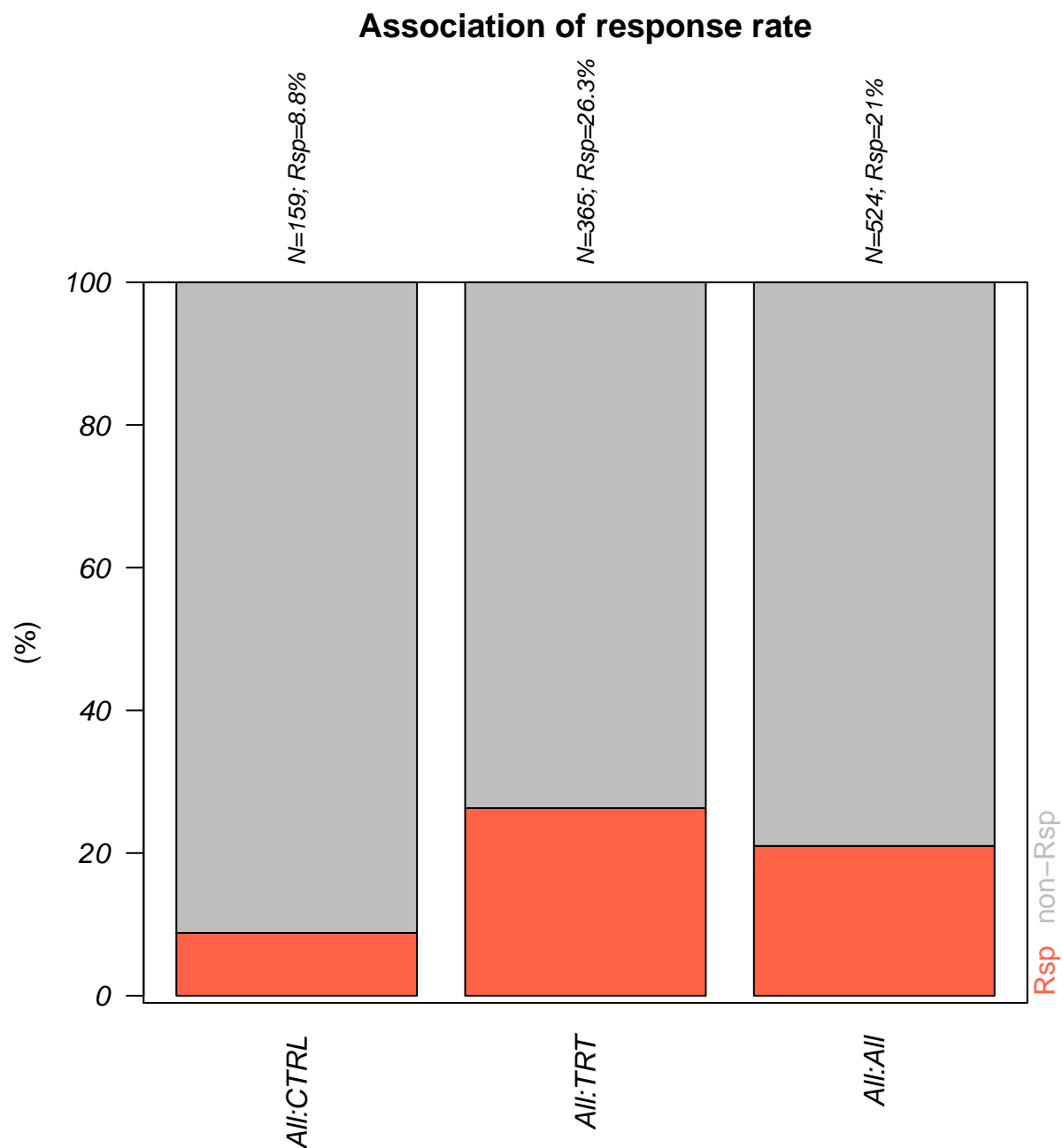
5.6 Compare full population vs BEP

```
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
```

Association of response rate
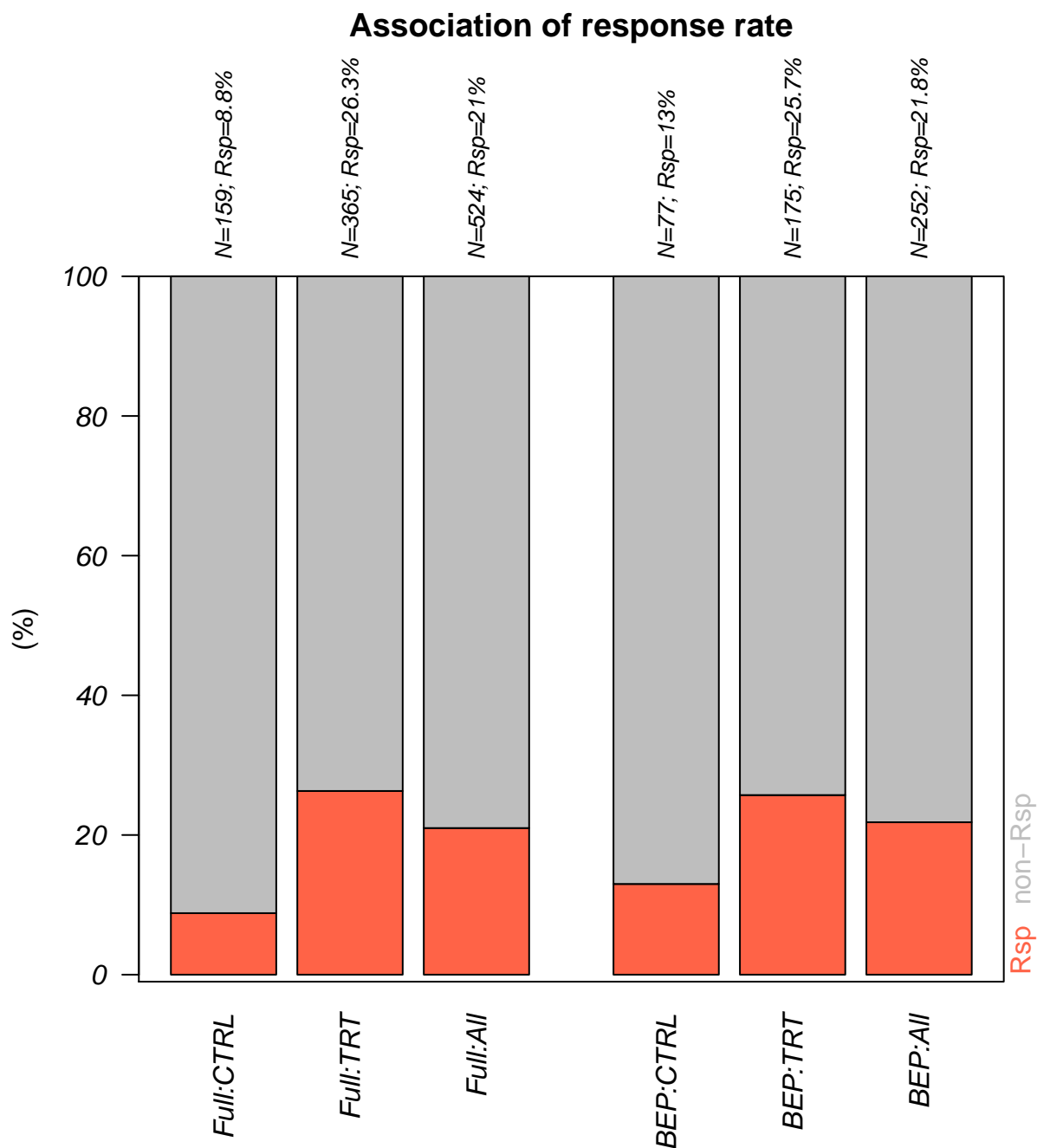
5.7 Compare subgroups

```
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`

Association of response rate
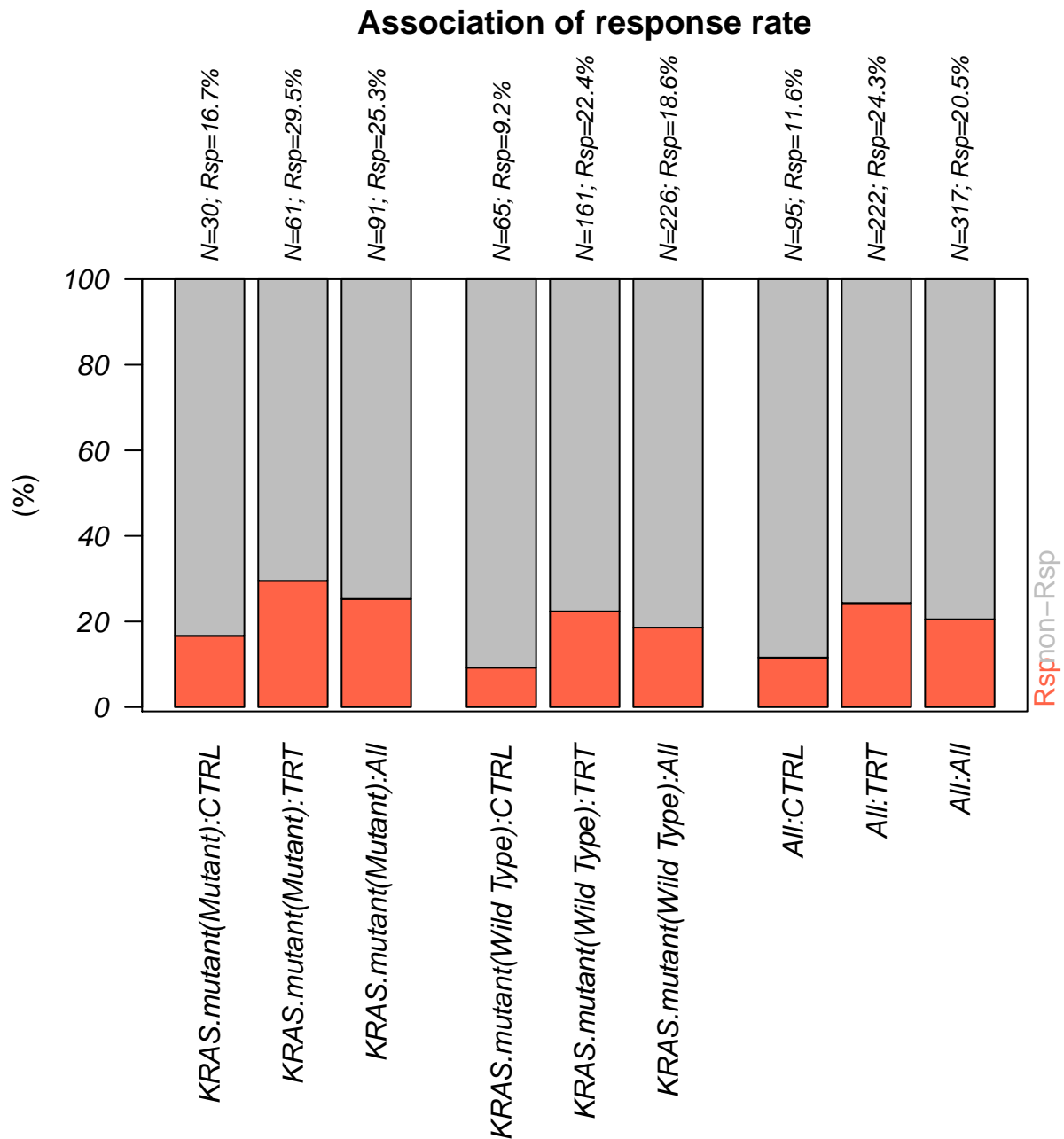
5.8 Plot count instead of percentage

```
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

Association of response rate
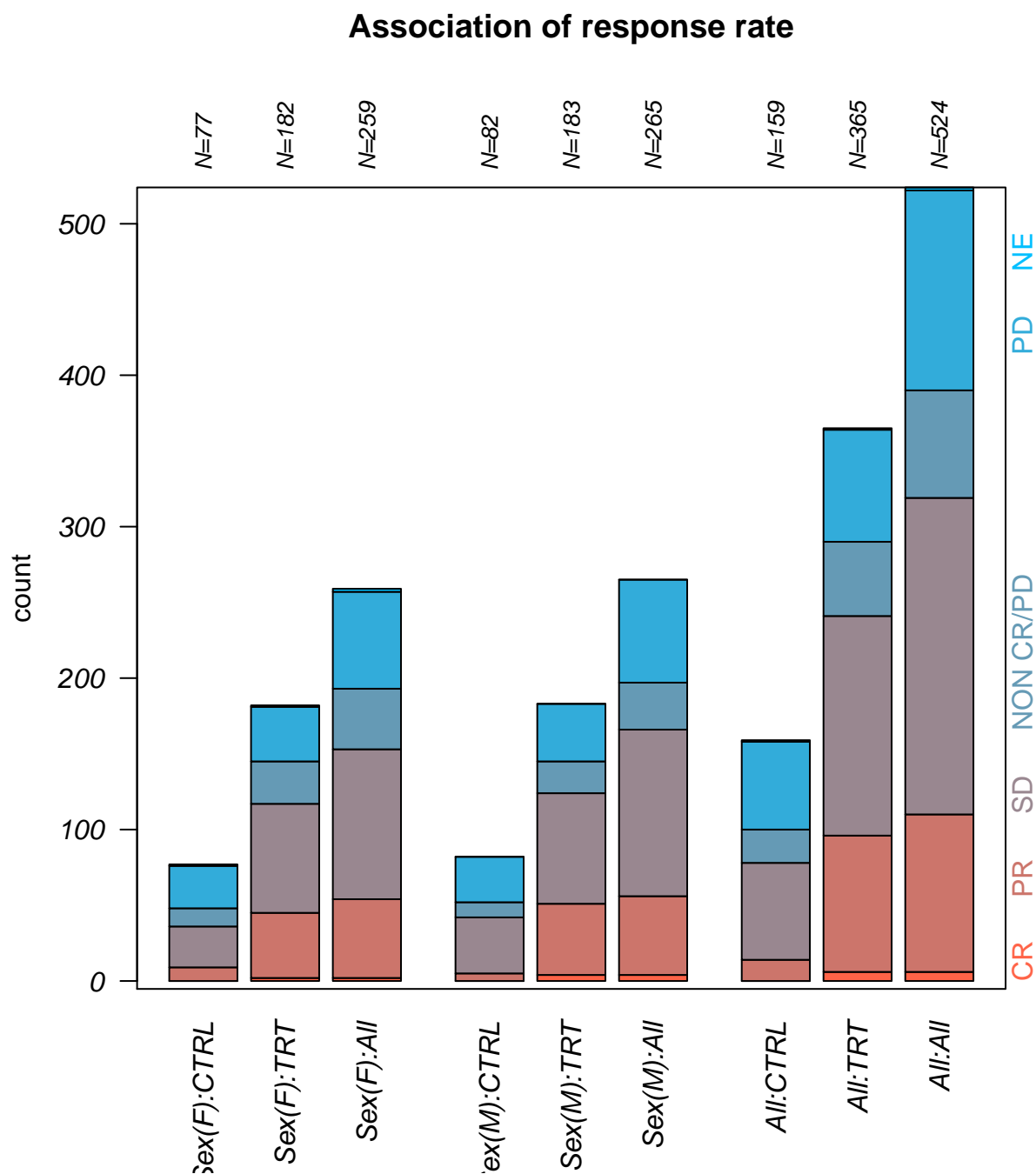
6 PlotKM(): Plot KM curves for subpopulations

6.1 Without subgroup

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

PFS ITT

550	417	274	128	71	30	10	0
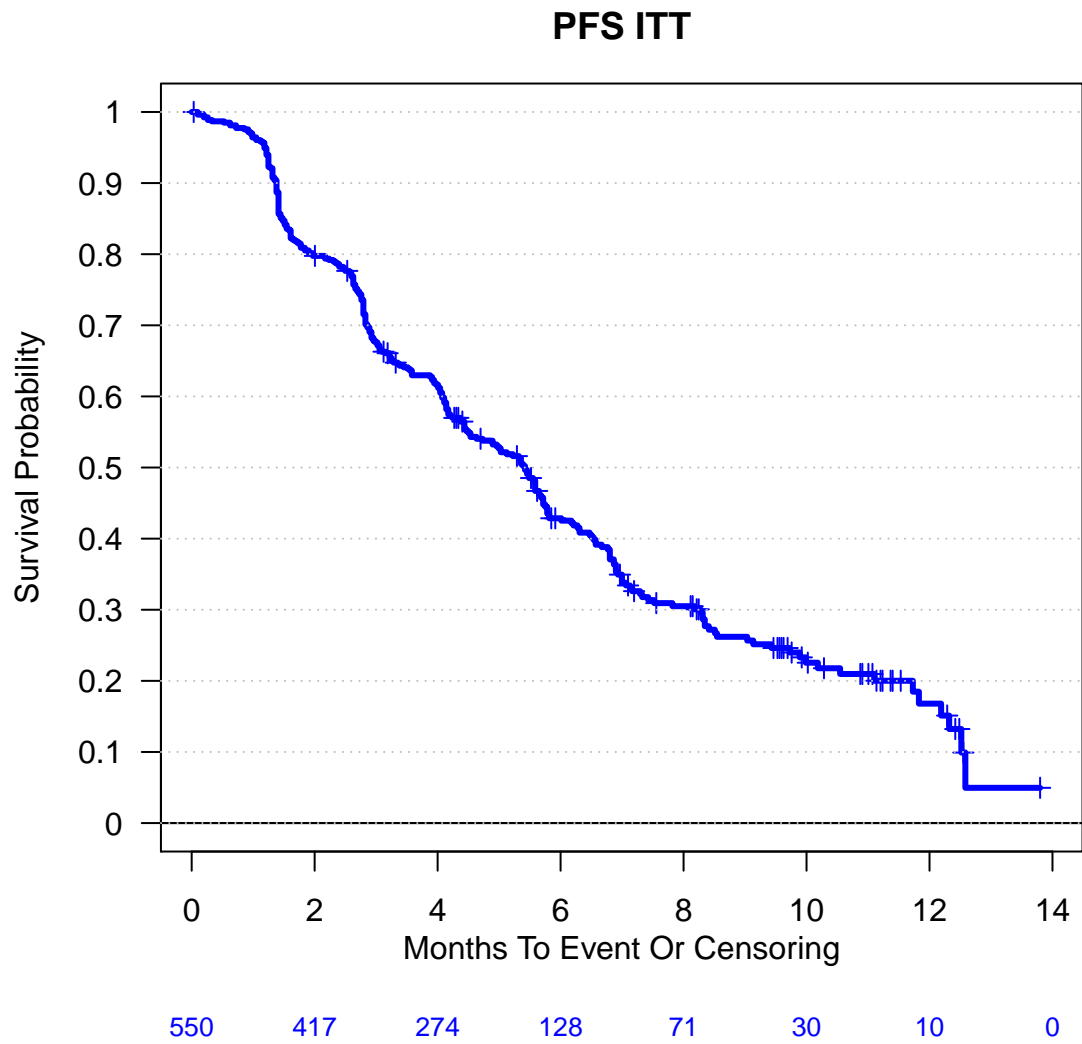
```
## [1] ""
```

6.2 Without subgroup, BEP

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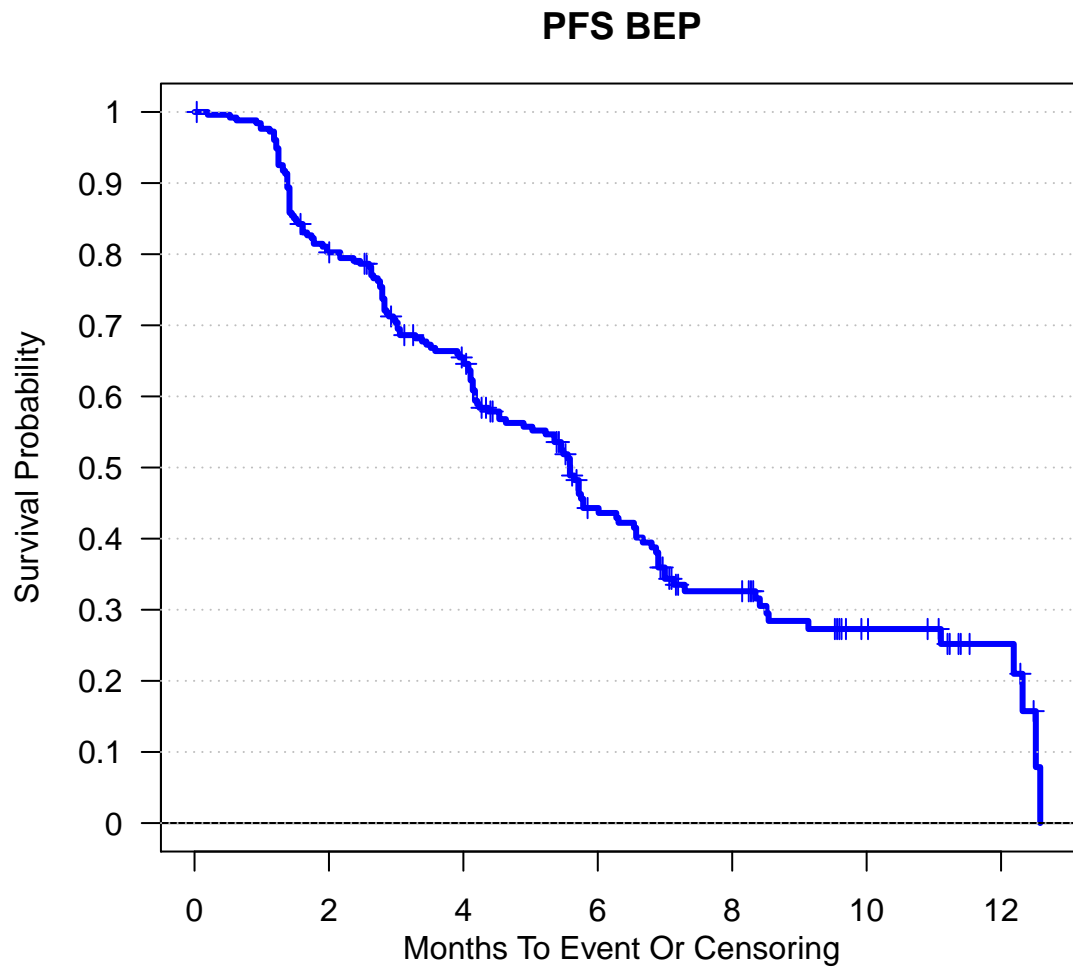
PFS BEP

| 257 | 201 | 145 | 64 | 36 | 16 | 6 |

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

6.3 By TRT

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

PFS ITT by treatment

	CTRL, MST 3.25
	TRT, MST 5.82
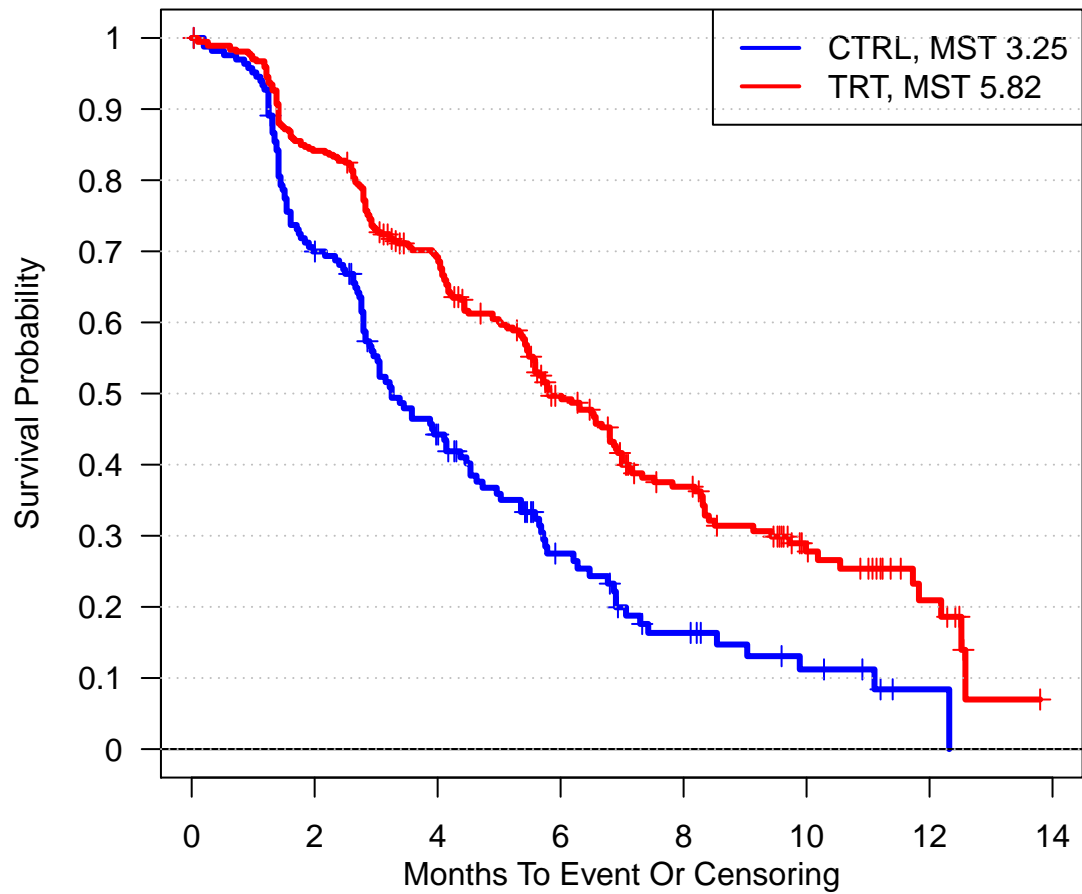
CTRL	182	112	58	26	13	6	1	0
TRT	368	305	216	102	58	24	9	0

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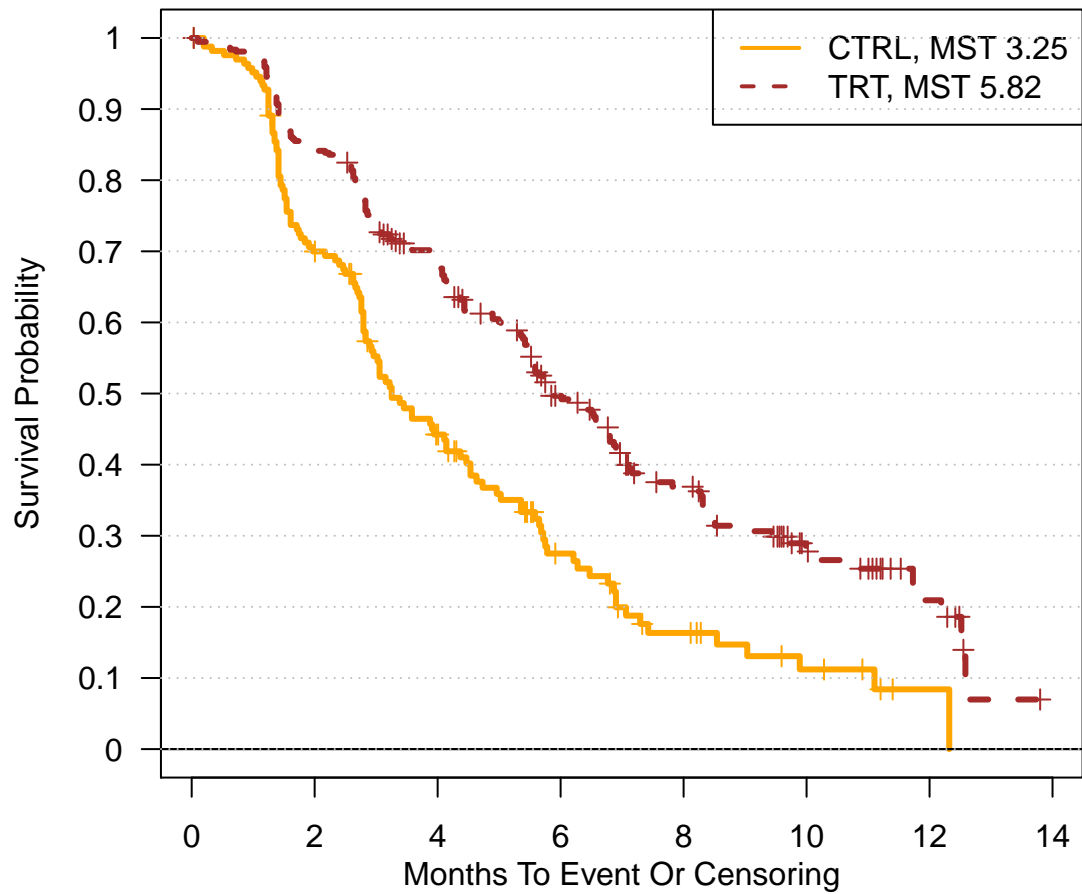
CTRL	182	112	58	26	13	6	1	0
TRT	368	305	216	102	58	24	9	0

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

6.5   Mark median PFS, no grid

```r
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
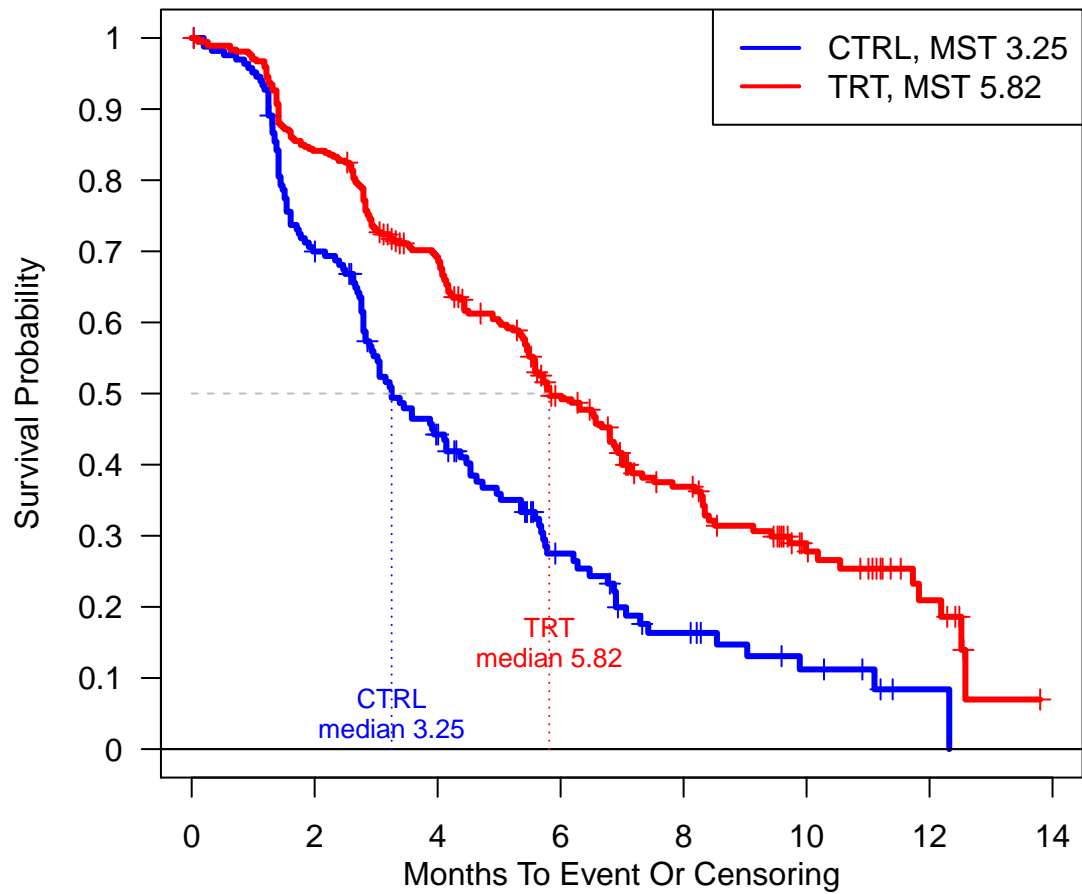

```
## [1] ""
```

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, MST 5.45
	- - -	Wild Type, MST 5.55
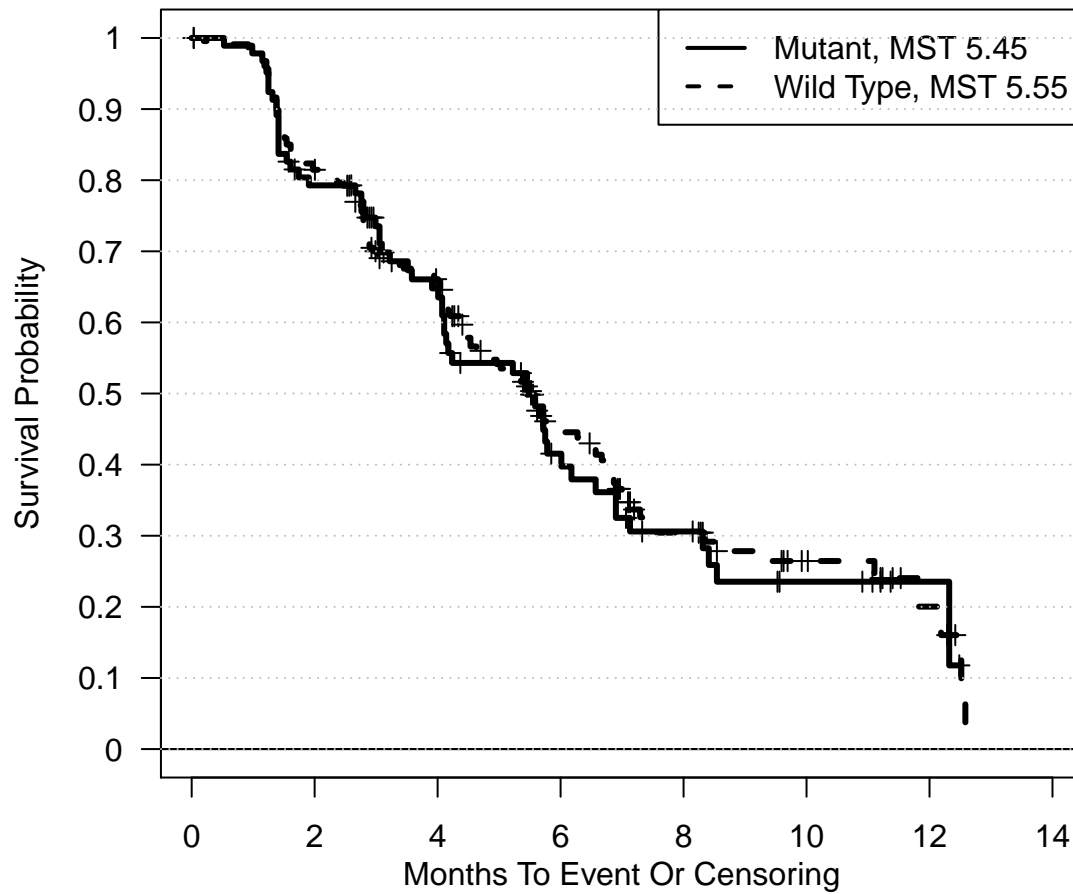
	0	2	4	6	8	10	12	14
Mutant	95	71	51	23	14	7	2	0
Wild Type	231	183	133	57	28	12	5	0

```
## [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
```
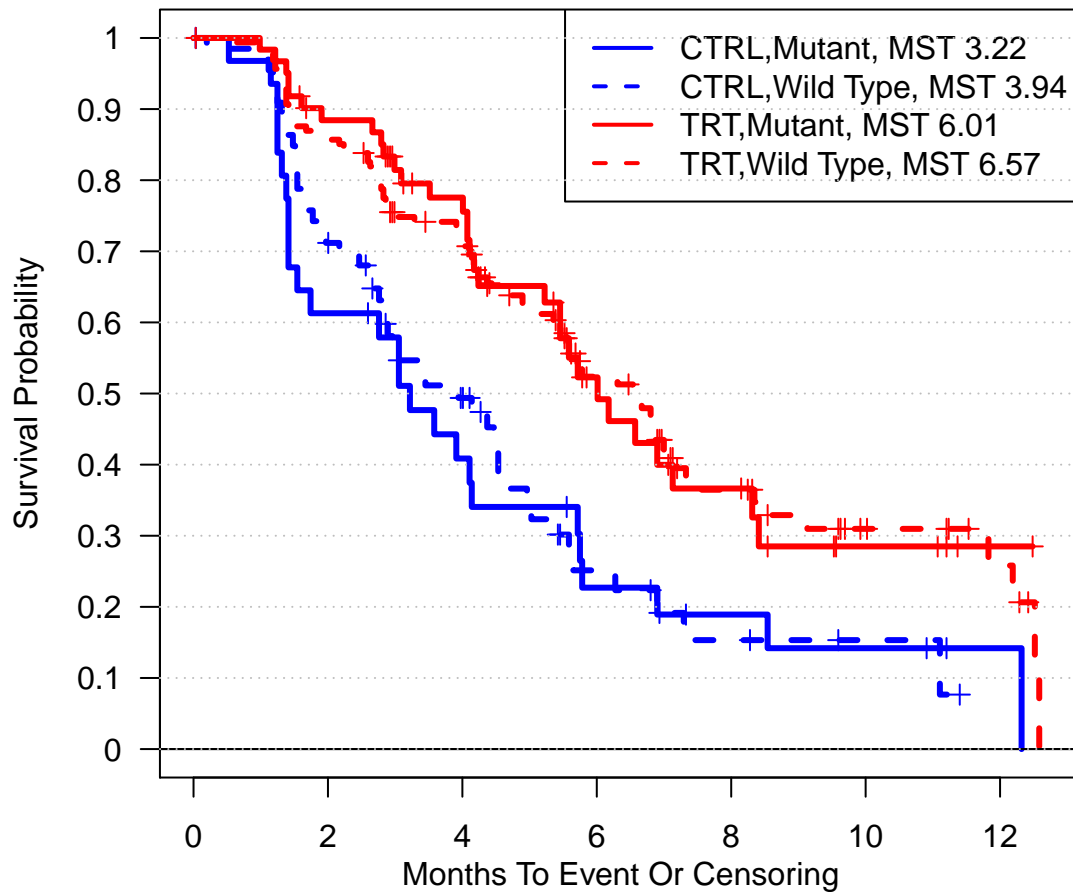
OS BEP by treatment, by KRAS mutation

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

```r
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
```
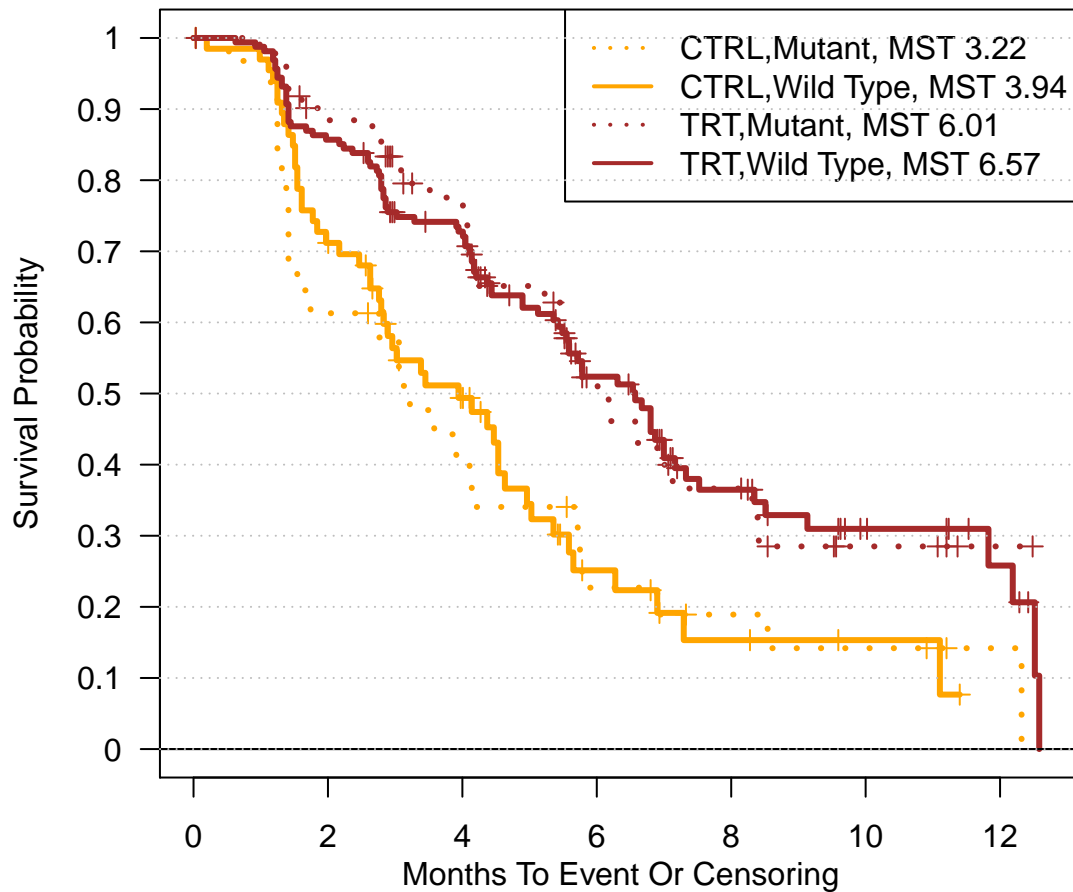
PFS BEP by treatment, by KRAS mutation

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="continuous",
        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

Legend:
- CTRL,[0–50%, 1.42–70.52), MST 3.91
- CTRL,[50–100%, 70.52–9541.5], MST 3.58
- TRT,[0–50%, 1.42–70.52), MST 5.42
- TRT,[50–100%, 70.52–9541.5], MST 7.16
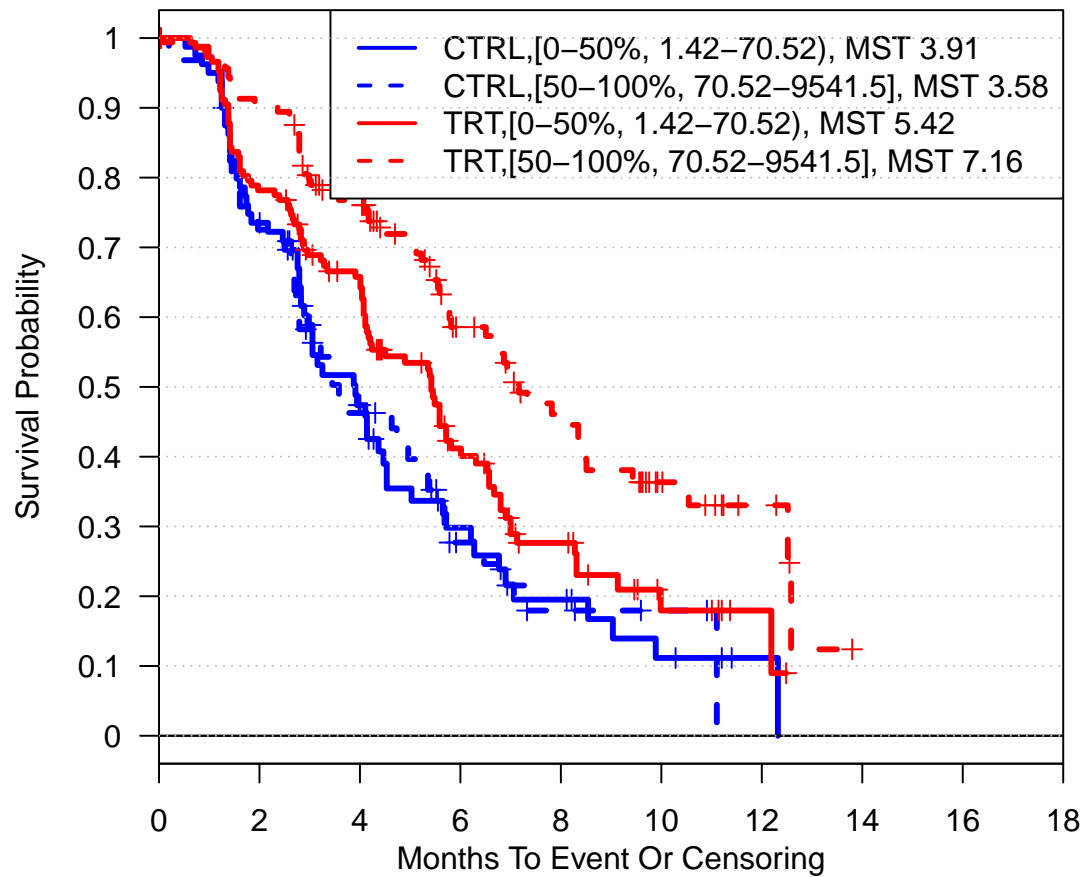
	0	2	4	6	8	10	12	14	16	18
CTRL,[0–50%, 1.42–70.52)	82	58	31	15	9	4	1	0	0	0
CTRL,[50–100%, 70.52–9541.5]	70	44	23	9	4	2	0	0	0	0
TRT,[0–50%, 1.42–70.52)	147	113	83	38	20	6	2	0	0	0
TRT,[50–100%, 70.52–9541.5]	162	145	105	47	30	12	5	0	0	0

```
## [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="continuous",
         numerical.cutoff=100)
         )
```

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

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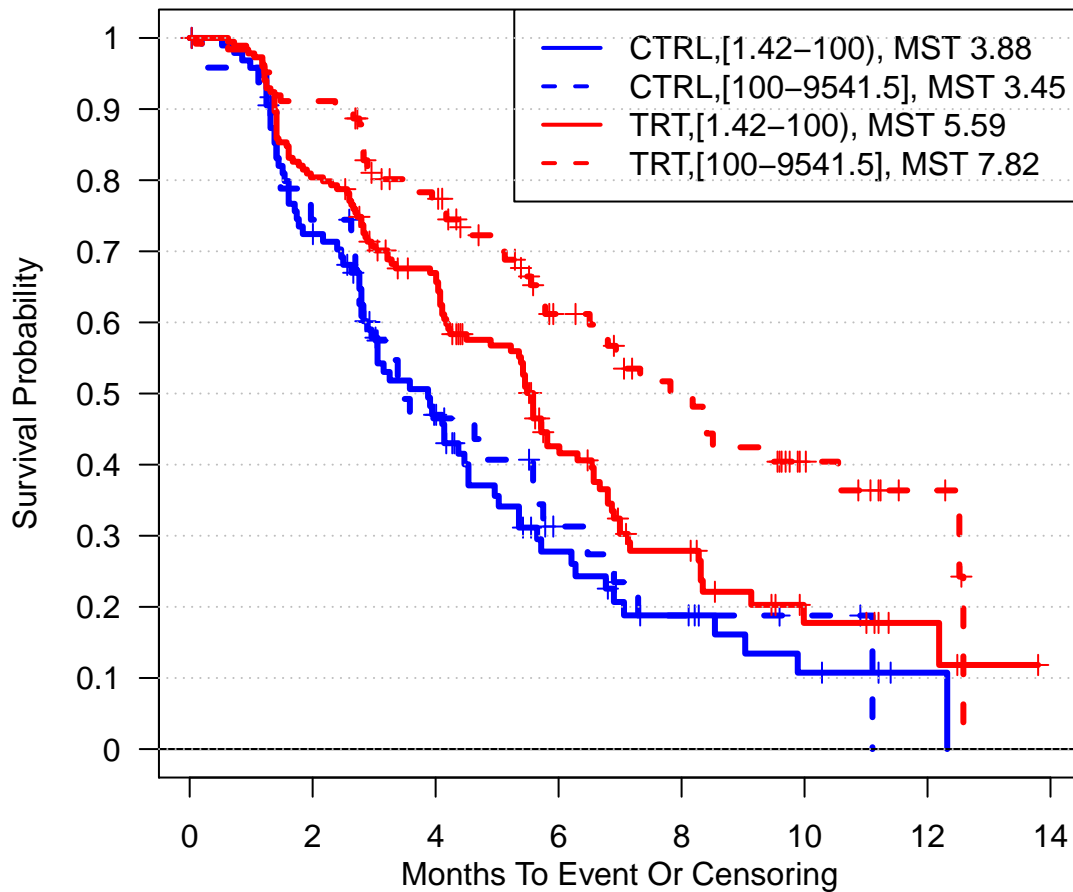
CTRL,[1.42–100)	99	68	37	16	9	4	1	0
CTRL,[100–9541.5]	53	34	17	8	4	2	0	0
TRT,[1.42–100)	184	146	104	43	22	7	3	0
TRT,[100–9541.5]	125	112	84	42	28	11	4	0

```
## [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="continuous",
        numerical.cutoff=100, equal.in.high = F)
        )
```

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

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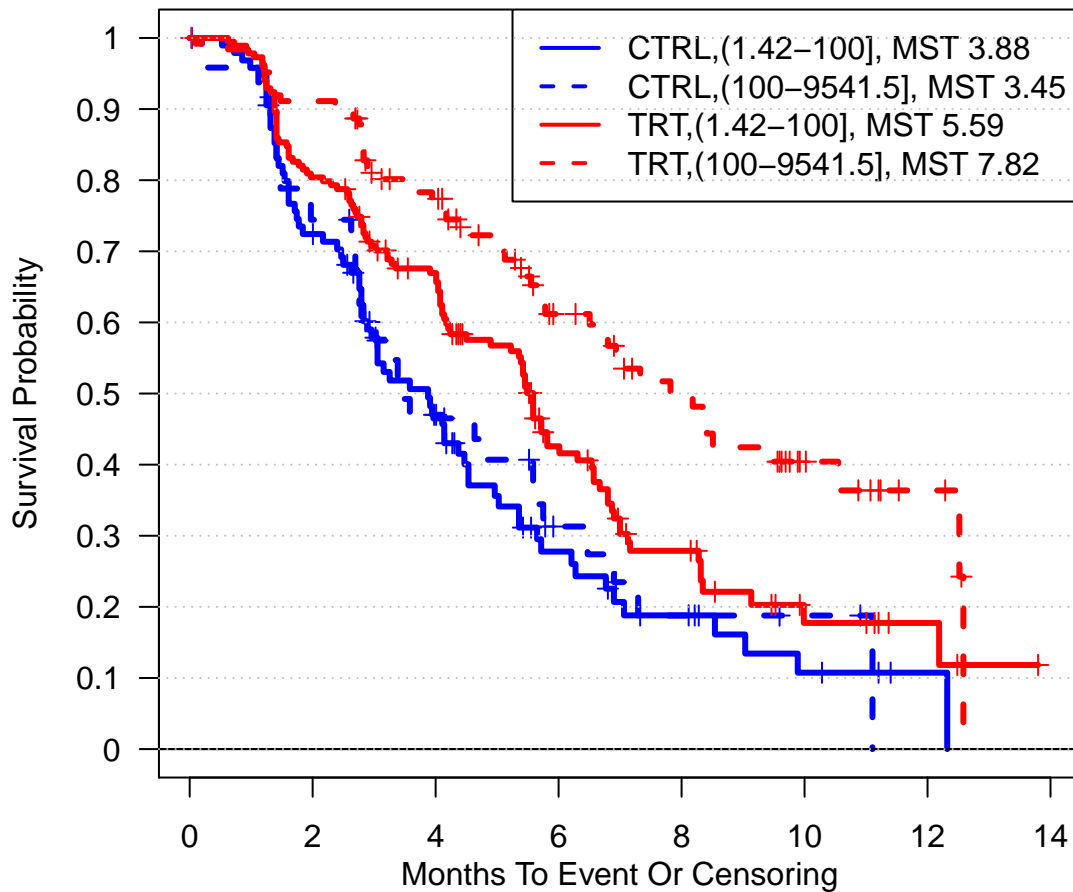
CTRL,(1.42–100]	99	68	37	16	9	4	1	0
CTRL,(100–9541.5]	53	34	17	8	4	2	0	0
TRT,(1.42–100]	184	146	104	43	22	7	3	0
TRT,(100–9541.5]	125	112	84	42	28	11	4	0

```
## [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="continuous",
          numerical.cutoff=c(100,500), xlim=c(0, 20))
          )
```

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

PFS BEP by treatment, by KRAS expression

Legend:
- CTRL,[1.42–100), MST 3.88
- CTRL,[100–500), MST 3.58
- CTRL,[500–9541.5], MST 2.76
- TRT,[1.42–100), MST 5.59
- TRT,[100–500), MST 8.18
- TRT,[500–9541.5], MST 10.55
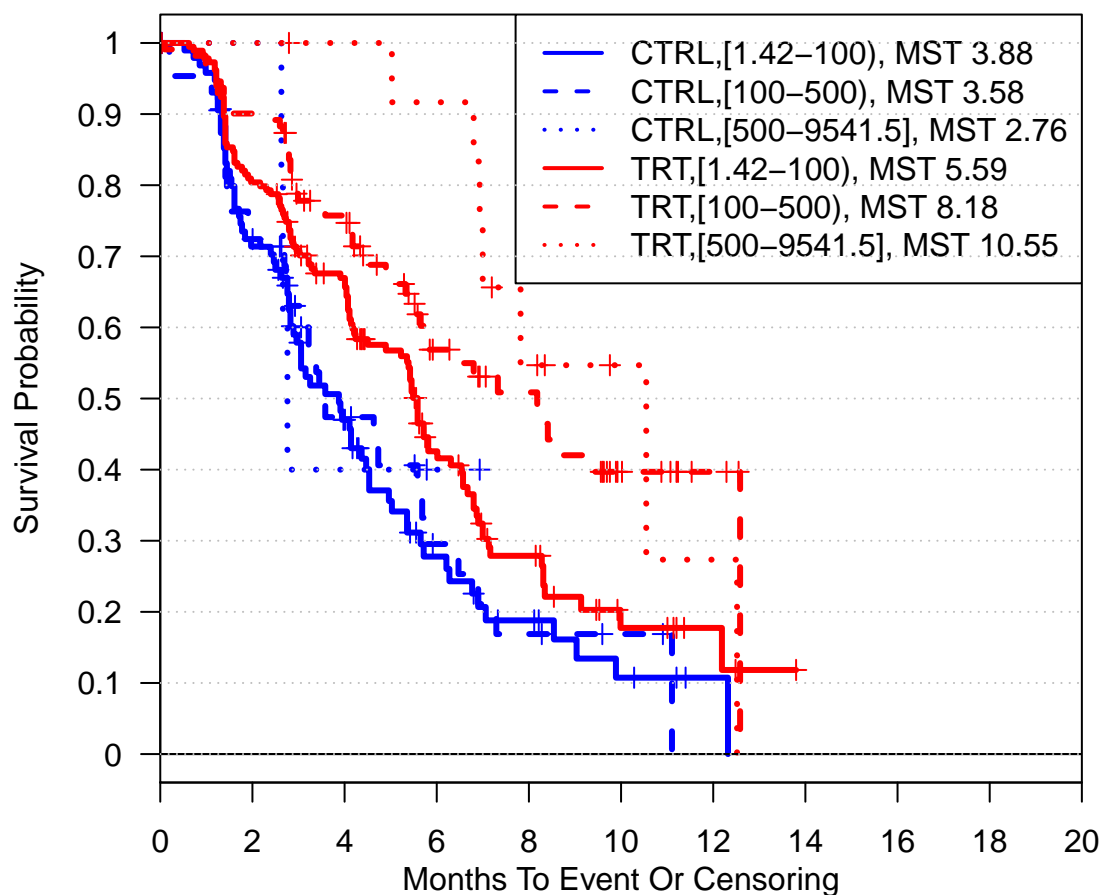
CTRL,[1.42–100)	99	68	37	16	9	4	1	0	0	0	0
CTRL,[100–500)	47	29	15	7	4	2	0	0	0	0	0
CTRL,[500–9541.5]	6	5	2	1	0	0	0	0	0	0	0
TRT,[1.42–100)	184	146	104	43	22	7	3	0	0	0	0
TRT,[100–500)	112	99	72	31	23	9	3	0	0	0	0
TRT,[500–9541.5]	13	13	12	11	5	2	1	0	0	0	0

```
## [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="continuous",
        numerical.cutoff=c(100,500),
        col=c("green","green","green","brown","brown","brown"),
        xlim=c(0,20))
        )
```

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

PFS BEP by treatment, by KRAS expression

Legend:
- CTRL,[1.42−100), MST 3.88
- CTRL,[100−500), MST 3.58
- CTRL,[500−9541.5], MST 2.76
- TRT,[1.42−100), MST 5.59
- TRT,[100−500), MST 8.18
- TRT,[500−9541.5], MST 10.55
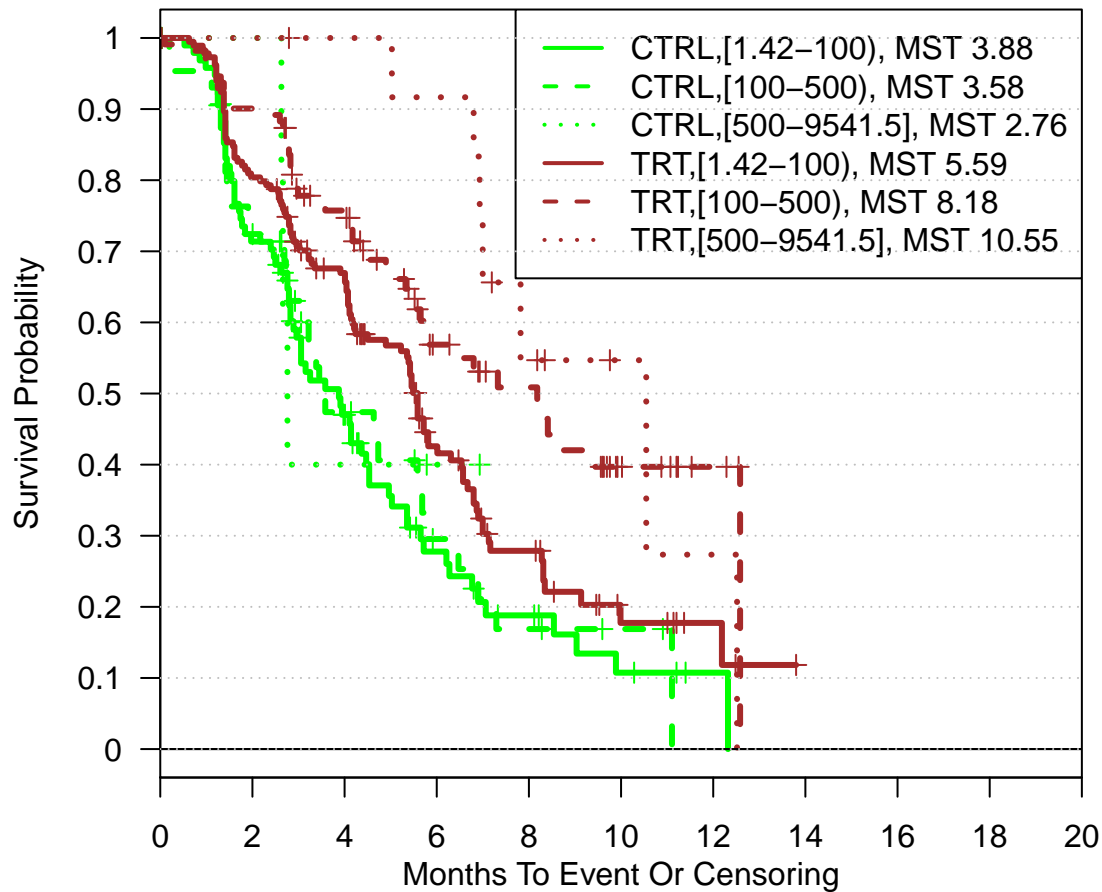
CTRL,[1.42−100)	99	68	37	16	9	4	1	0	0	0	0
CTRL,[100−500)	47	29	15	7	4	2	0	0	0	0	0
CTRL,[500−9541.5]	6	5	2	1	0	0	0	0	0	0	0
TRT,[1.42−100)	184	146	104	43	22	7	3	0	0	0	0
TRT,[100−500)	112	99	72	31	23	9	3	0	0	0	0
TRT,[500−9541.5]	13	13	12	11	5	2	1	0	0	0	0

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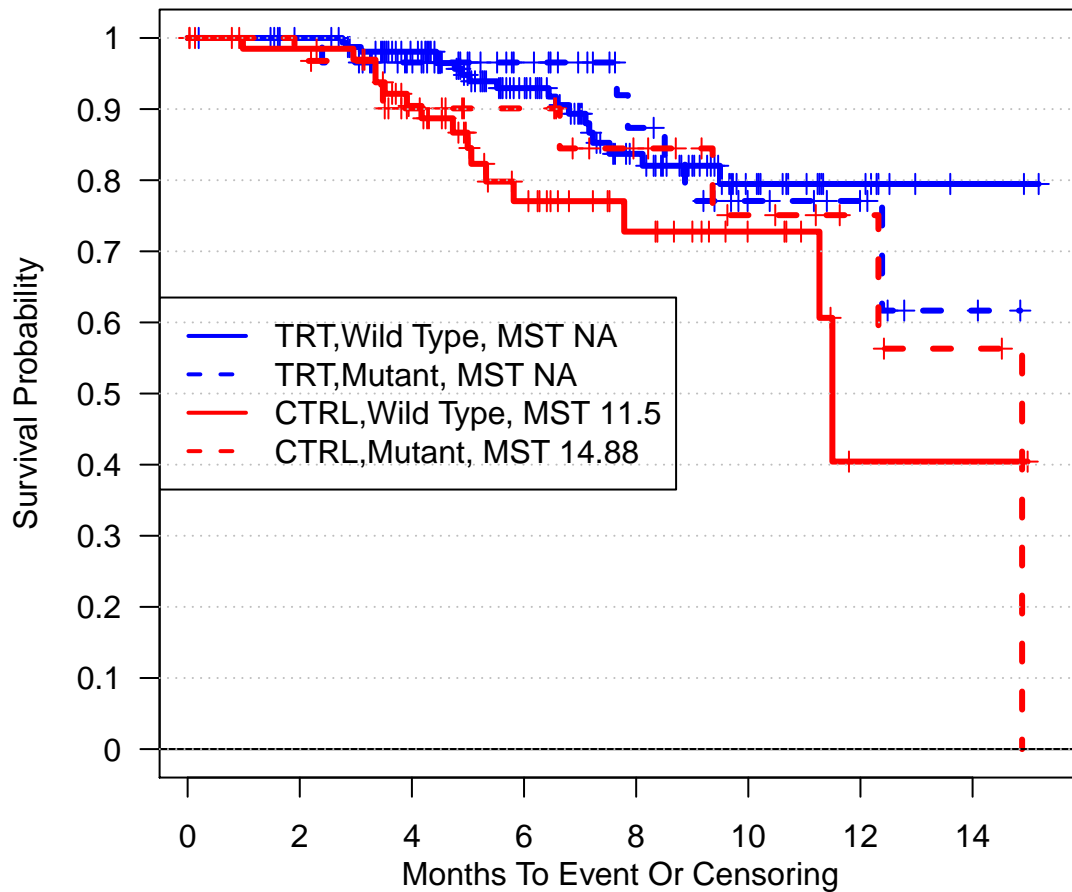
TRT,Wild Type	162	159	137	87	50	22	10	2
TRT,Mutant	61	58	48	31	19	10	6	2
CTRL,Wild Type	69	65	52	28	17	9	1	1
CTRL,Mutant	34	30	23	18	12	7	4	2

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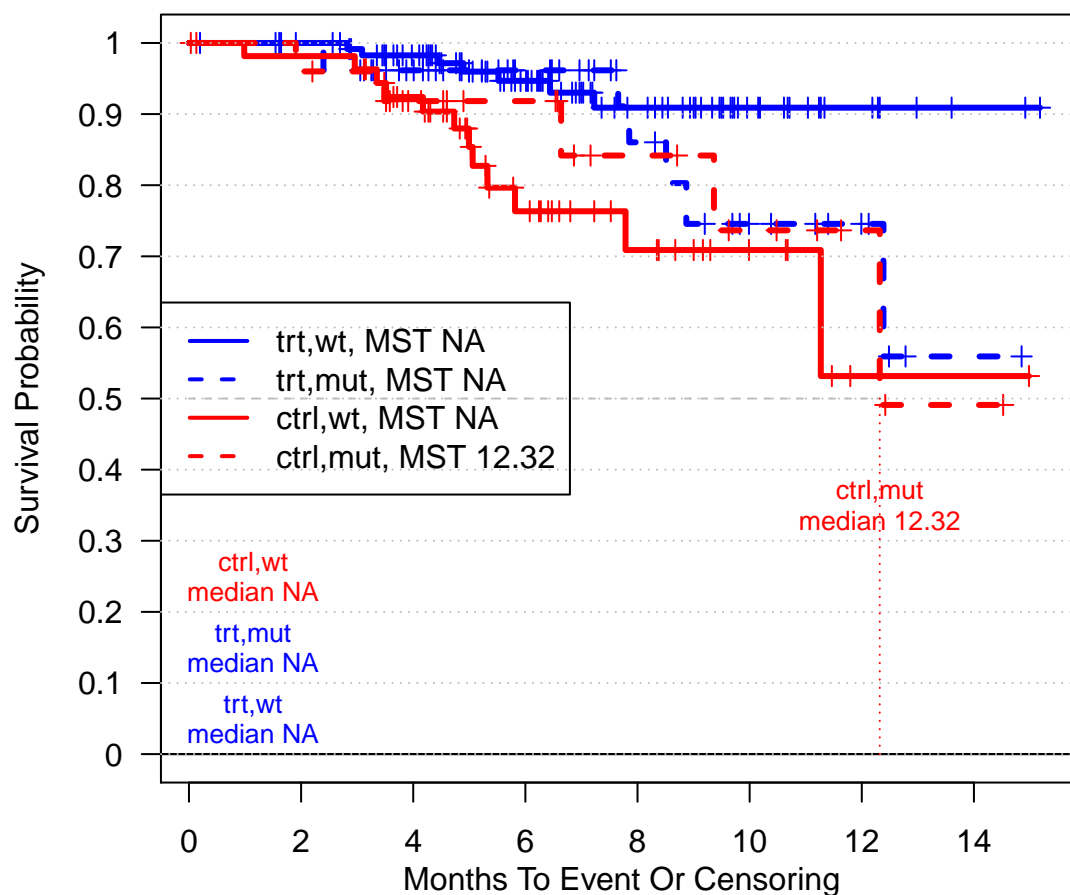
trt,wt	121	119	101	66	38	17	7	2
trt,mut	55	52	43	28	17	9	5	1
ctrl,wt	56	53	45	23	13	6	1	1
ctrl,mut	25	24	18	14	9	6	3	1

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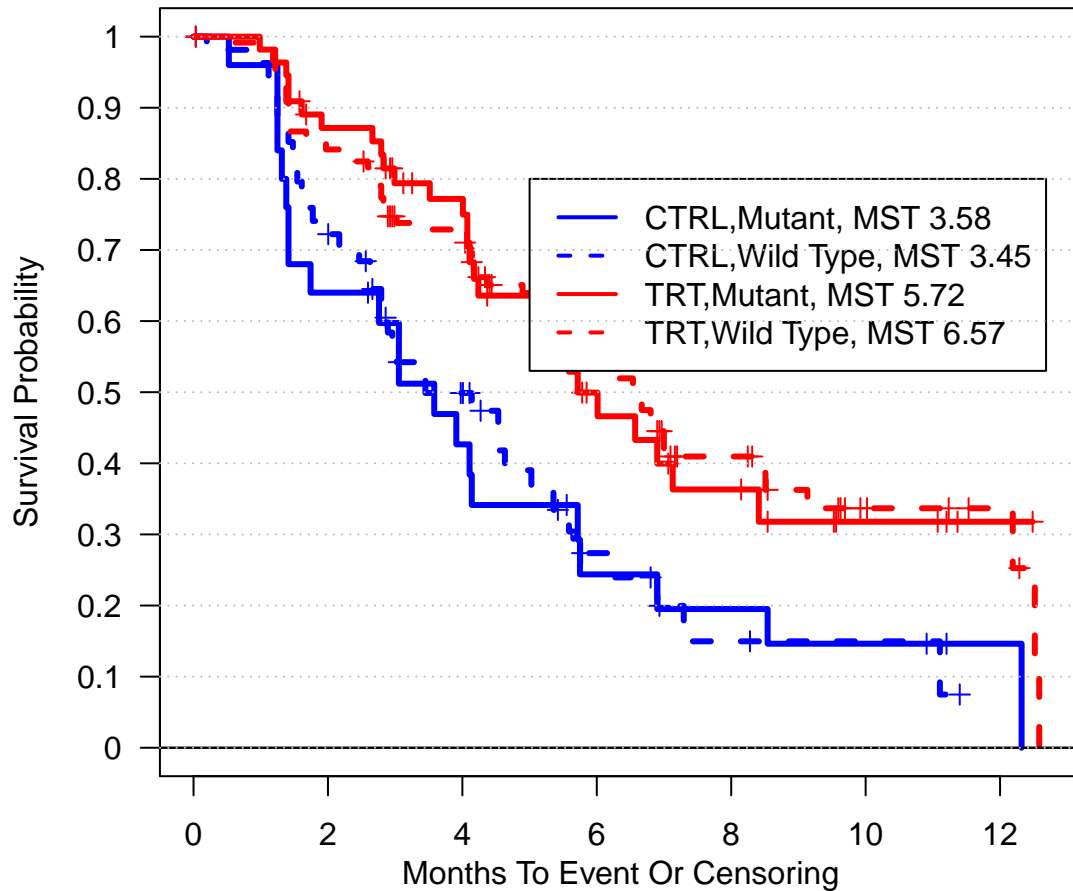
CTRL,Mutant	25	16	10	5	4	3	1
CTRL,Wild Type	56	39	22	8	3	2	0
TRT,Mutant	55	46	35	15	9	4	1
TRT,Wild Type	121	100	78	36	20	7	4

```
## [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")
```

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	73 / 103	3.58			
	TRT	118 / 223	6.54	0.5	(0.37 – 0.66)	2.8e–06
KRAS.mutant(Mutant)	CTRL	26 / 34	3.22			
	TRT	31 / 61	6.01	0.48	(0.28 – 0.8)	0.0055
KRAS.mutant(Wild Type)	CTRL	47 / 69	3.94			
	TRT	87 / 162	6.57	0.5	(0.35 – 0.72)	0.00019


```
                                  0.28 0.53  1.0  1.89 3.57
                          <--  TRT better [HR]  CTRL bette
                               unadj P = 0.87(interaction)
```

```
##                               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" "7.8e-08"
## [4,] ""            ""
## [5,] "0.37 - 0.66" "2.8e-06"
## [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

Subgroup	Group	Event/N	MST	HR	CI	raw P	Forest plot
							TRT better / CTRL better
All	CTRL	120 / 182	3.25				
	TRT	202 / 368	5.82	0.54	0.43 – 0.67	7.8e–08	
BEP	CTRL	73 / 103	3.58				
	TRT	118 / 223	6.54	0.5	0.37 – 0.66	2.8e–06	
KRAS.mutant(Mutant)	CTRL	26 / 34	3.22				
	TRT	31 / 61	6.01	0.48	0.28 – 0.8	0.0055	
KRAS.mutant(Wild Type)	CTRL	47 / 69	3.94				
	TRT	87 / 162	6.57	0.5	0.35 – 0.72	0.00019	

unadj P = 0.87(interaction)

Unadjusted, unstratified analysis

0.28   0.53   1   1.89   3.57

```
##                                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" "7.8e-08"
## [4,] ""            ""
## [5,] "0.37 - 0.66" "2.8e-06"
## [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, rename 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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	59 / 81	3.58			
	TRT	91 / 176	6.54	0.49	(0.36 – 0.69)	3.1e–05
KRAS.mutant(Mutant)	CTRL	21 / 25	3.58			
	TRT	28 / 55	5.72	0.49	(0.28 – 0.86)	0.013
KRAS.mutant(Wild Type)	CTRL	38 / 56	3.45			
	TRT	63 / 121	6.57	0.5	(0.33 – 0.75)	0.00093

```
                    0.28  0.53  1.0  1.89 3.57
              <–– TRT better [HR] CTRL bette
                  unadj P = 0.98(interaction)
```

```
##                              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" "7.8e-08"
```

```
## [4,] ""              ""
## [5,] "0.36 - 0.69" "3.1e-05"
## [6,] ""              ""
## [7,] "0.28 - 0.86" "0.013"
## [8,] ""              ""
## [9,] "0.33 - 0.75" "0.00093"
```

```r
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

```
##                          code.v
## [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
```

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	102 / 152	3.58			
	TRT	167 / 309	6.01	0.56	(0.43 – 0.71)	3.5e–06
KRAS exprs(>=25%, 23.26)	CTRL	73 / 111	3.38			
	TRT	112 / 236	6.93	0.45	(0.33 – 0.61)	1.5e–07
KRAS exprs(>=50%, 70.52)	CTRL	43 / 70	3.58			
	TRT	73 / 162	7.16	0.42	(0.29 – 0.62)	9.6e–06
KRAS exprs(>=75%, 177.29)	CTRL	22 / 37	4.73			
	TRT	33 / 79	8.41	0.38	(0.22 – 0.66)	0.00054

```
0.22        0.47    1.0      2.13     4.55
    <–– TRT better [HR] CTRL better ––>
```

```
##                                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" "7.8e-08"
##  [4,] ""           ""
##  [5,] "0.43 - 0.71" "3.5e-06"
##  [6,] ""           ""
##  [7,] "0.33 - 0.61" "1.5e-07"
##  [8,] ""           ""
##  [9,] "0.29 - 0.62" "9.6e-06"
## [10,] ""           ""
## [11,] "0.22 - 0.66" "0.00054"
```

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

```r
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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	59 / 81	3.58			
	TRT	91 / 176	6.54	0.49	(0.36 – 0.69)	3.1e–05
KRAS exprs(<25%, 22.63)	CTRL	16 / 22	4.14			
	TRT	30 / 42	5.45	0.7	(0.37 – 1.32)	0.27
KRAS exprs(<50%, 63.56)	CTRL	32 / 44	4.11			
	TRT	52 / 84	5.72	0.68	(0.43 – 1.06)	0.09
KRAS exprs(<75%, 170.07)	CTRL	44 / 61	3.91			
	TRT	75 / 131	5.59	0.61	(0.42 – 0.89)	0.0098

```
          0.36      0.60     1.0      1.67    2.78
              <-- TRT better [HR] CTRL better -->
```
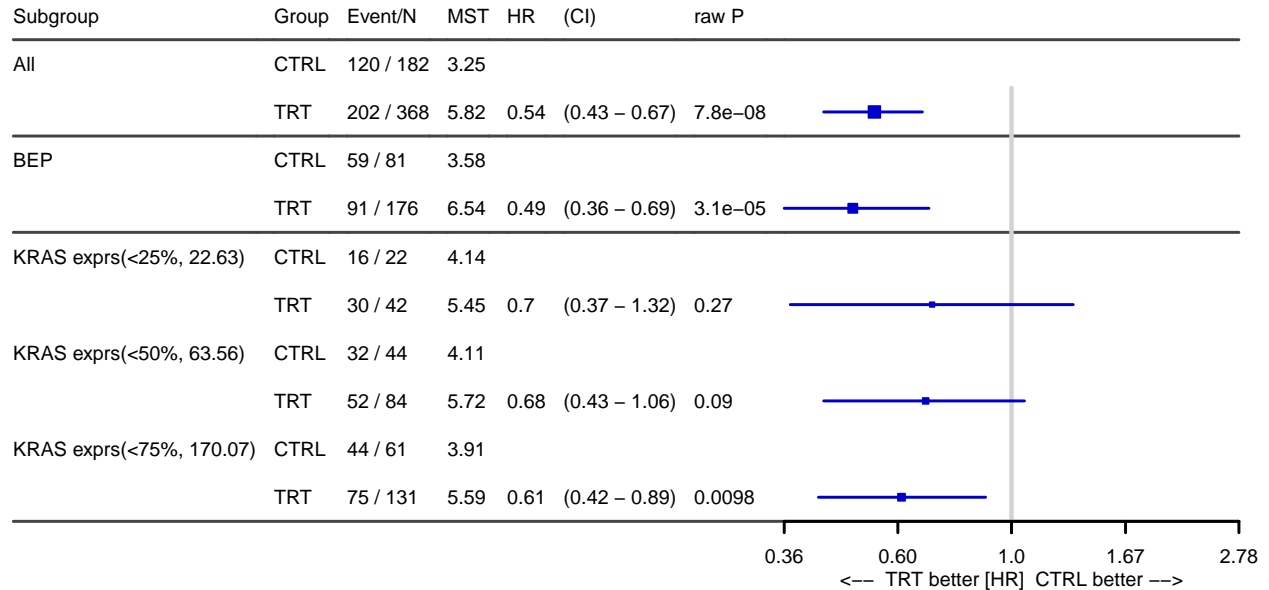
```
##                                code.v
## [1,] "Subgroup"               "Group" "Event/N"    "MST"   "HR"
## [2,] "All"                     "CTRL"  "120 / 182"  "3.25"  ""
## [3,] ""                        "TRT"   "202 / 368"  "5.82"  "0.54"
## [4,] "BEP"                     "CTRL"  "59 / 81"    "3.58"  ""
## [5,] ""                        "TRT"   "91 / 176"   "6.54"  "0.49"
## [6,] "KRAS exprs(<25%, 22.63)"  "CTRL"  "16 / 22"    "4.14"  ""
## [7,] ""                        "TRT"   "30 / 42"    "5.45"  "0.7"
## [8,] "KRAS exprs(<50%, 63.56)"  "CTRL"  "32 / 44"    "4.11"  ""
## [9,] ""                        "TRT"   "52 / 84"    "5.72"  "0.68"
## [10,] "KRAS exprs(<75%, 170.07)" "CTRL"  "44 / 61"    "3.91"  ""
## [11,] ""                        "TRT"   "75 / 131"   "5.59"  "0.61"
##
## [1,] "CI"           "raw P"
## [2,] ""             ""
## [3,] "0.43 - 0.67" "7.8e-08"
## [4,] ""             ""
## [5,] "0.36 - 0.69" "3.1e-05"
## [6,] ""             ""
## [7,] "0.37 - 1.32" "0.27"
## [8,] ""             ""
## [9,] "0.43 - 1.06" "0.09"
## [10,] ""             ""
## [11,] "0.42 - 0.89" "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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	102 / 152	3.58			
	TRT	167 / 309	6.01	0.56	(0.43 – 0.71)	3.5e–06
KRAS exprs(>=25%, 23.26)	CTRL	73 / 111	3.38			
	TRT	112 / 236	6.93	0.45	(0.33 – 0.61)	1.5e–07
KRAS exprs(>=50%, 70.52)	CTRL	43 / 70	3.58			
	TRT	73 / 162	7.16	0.42	(0.29 – 0.62)	9.6e–06
KRAS exprs(>=75%, 177.29)	CTRL	22 / 37	4.73			
	TRT	33 / 79	8.41	0.38	(0.22 – 0.66)	0.00054
KRAS exprs(<25%, 23.26)	CTRL	29 / 41	3.94			
	TRT	55 / 73	4.07	1.04	(0.66 – 1.64)	0.87
KRAS exprs(<50%, 70.52)	CTRL	59 / 82	3.91			
	TRT	94 / 147	5.42	0.73	(0.53 – 1.01)	0.06
KRAS exprs(<75%, 177.29)	CTRL	80 / 115	3.58			
	TRT	134 / 230	5.59	0.63	(0.48 – 0.84)	0.0013

```
0.22        0.47        1.0        2.13        4.55
        <-- TRT better [HR] CTRL better -->
```

```
##                                 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"
## [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" "7.8e-08"
##  [4,] ""            ""
##  [5,] "0.43 - 0.71" "3.5e-06"
##  [6,] ""            ""
##  [7,] "0.33 - 0.61" "1.5e-07"
##  [8,] ""            ""
##  [9,] "0.29 - 0.62" "9.6e-06"
## [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:

```r
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
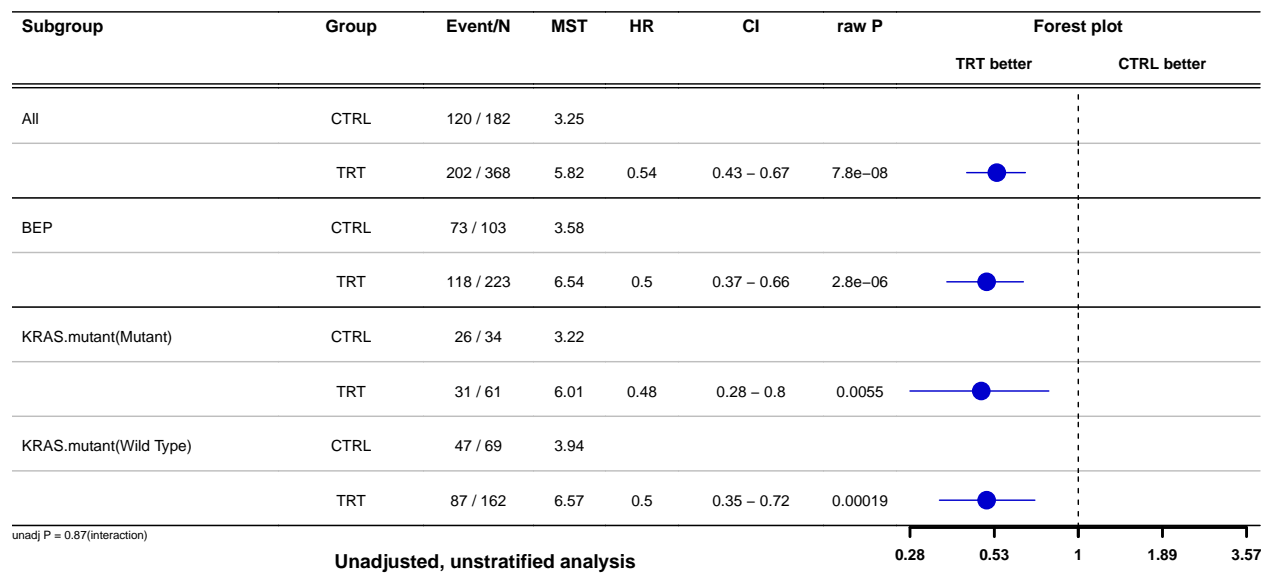**PFS, KRAS exprs**
Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e−08
BEP	CTRL	102 / 152	3.58			
	TRT	167 / 309	6.01	0.56	(0.43 – 0.71)	3.5e−06
KRAS exprs(>=25%, 23.26)	CTRL	73 / 111	3.38			
	TRT	112 / 236	6.93	0.45	(0.33 – 0.61)	1.5e−07
KRAS exprs(<25%, 23.26)	CTRL	29 / 41	3.94			
	TRT	55 / 73	4.07	1.04	(0.66 – 1.64)	0.87
KRAS exprs(>=50%, 70.52)	CTRL	43 / 70	3.58			
	TRT	73 / 162	7.16	0.42	(0.29 – 0.62)	9.6e−06
KRAS exprs(<50%, 70.52)	CTRL	59 / 82	3.91			
	TRT	94 / 147	5.42	0.73	(0.53 – 1.01)	0.06
KRAS exprs(>=75%, 177.29)	CTRL	22 / 37	4.73			
	TRT	33 / 79	8.41	0.38	(0.22 – 0.66)	0.00054
KRAS exprs(<75%, 177.29)	CTRL	80 / 115	3.58			
	TRT	134 / 230	5.59	0.63	(0.48 – 0.84)	0.0013

```
0.22      0.47    1.0    2.13    4.55
   <−− TRT better [HR]  CTRL better −−>
```

```
##                                  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(<25%, 23.26)"   "CTRL"  "29 / 41"   "3.94"  ""
## [9,] ""                          "TRT"   "55 / 73"   "4.07"  "1.04"
## [10,] "KRAS exprs(>=50%, 70.52)" "CTRL"  "43 / 70"   "3.58"  ""
## [11,] ""                         "TRT"   "73 / 162"  "7.16"  "0.42"
## [12,] "KRAS exprs(<50%, 70.52)"  "CTRL"  "59 / 82"   "3.91"  ""
## [13,] ""                         "TRT"   "94 / 147"  "5.42"  "0.73"
## [14,] "KRAS exprs(>=75%, 177.29)" "CTRL" "22 / 37"   "4.73"  ""
## [15,] ""                         "TRT"   "33 / 79"   "8.41"  "0.38"
## [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" "7.8e-08"
## [4,] ""             ""
## [5,] "0.43 - 0.71" "3.5e-06"
## [6,] ""             ""
## [7,] "0.33 - 0.61" "1.5e-07"
## [8,] ""             ""
## [9,] "0.66 - 1.64" "0.87"
```
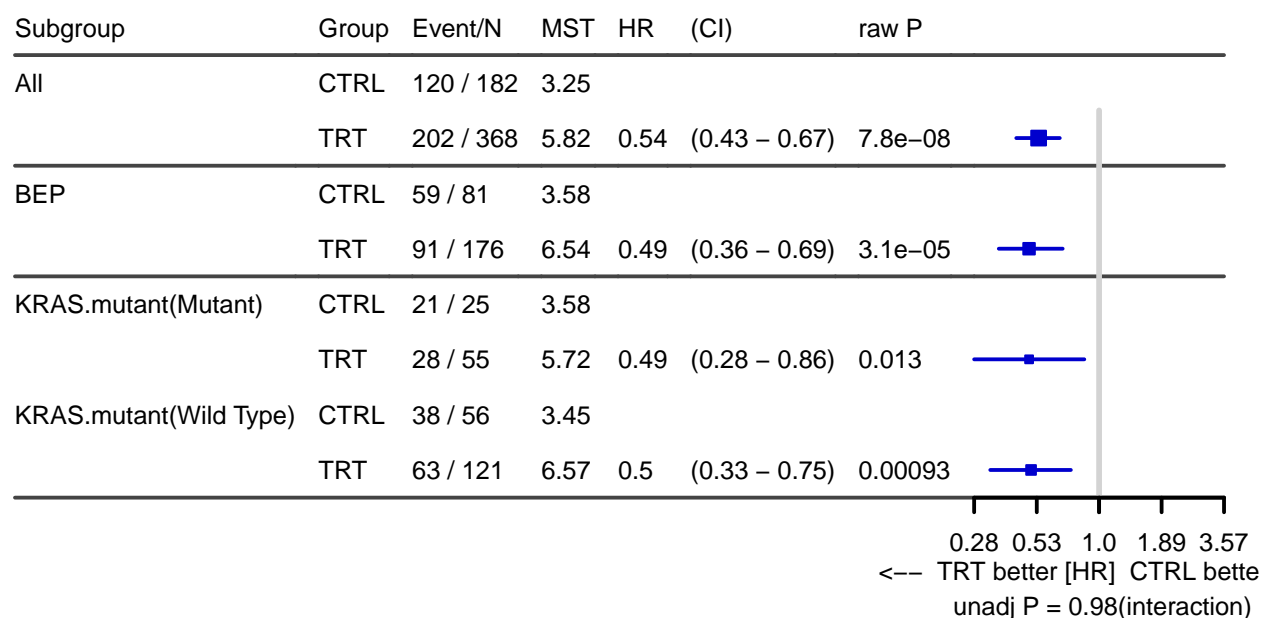
```
## [10,] ""              ""
## [11,] "0.29 - 0.62" "9.6e-06"
## [12,] ""              ""
## [13,] "0.53 - 1.01" "0.06"
## [14,] ""              ""
## [15,] "0.22 - 0.66" "0.00054"
## [16,] ""              ""
## [17,] "0.48 - 0.84" "0.0013"
```

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

```r
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
```

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	102 / 152	3.58			
	TRT	167 / 309	6.01	0.56	(0.43 – 0.71)	3.5e–06
KRAS exprs[0–25%, 1.41–23.26)	CTRL	29 / 41	3.94			
	TRT	55 / 73	4.07	1.04	(0.66 – 1.64)	0.87
KRAS exprs[25–50%, 23.26–70.52)	CTRL	30 / 41	3.15			
	TRT	39 / 74	6.67	0.51	(0.31 – 0.82)	0.0057
KRAS exprs[50–75%, 70.52–177.29)	CTRL	21 / 33	3.22			
	TRT	40 / 83	5.82	0.46	(0.27 – 0.79)	0.0049
KRAS exprs[75–100%, 177.29–9541.51]	CTRL	22 / 37	4.73			
	TRT	33 / 79	8.41	0.38	(0.22 – 0.66)	0.00054

```
        0.22    0.47    1.0    2.13   4.55
        <–– TRT better [HR]  CTRL better ––>
```

```
##                                       code.v
## [1,] "Subgroup"                       "Group" "Event/N"     "MST"
## [2,] "All"                            "CTRL"  "120 / 182" "3.25"
```
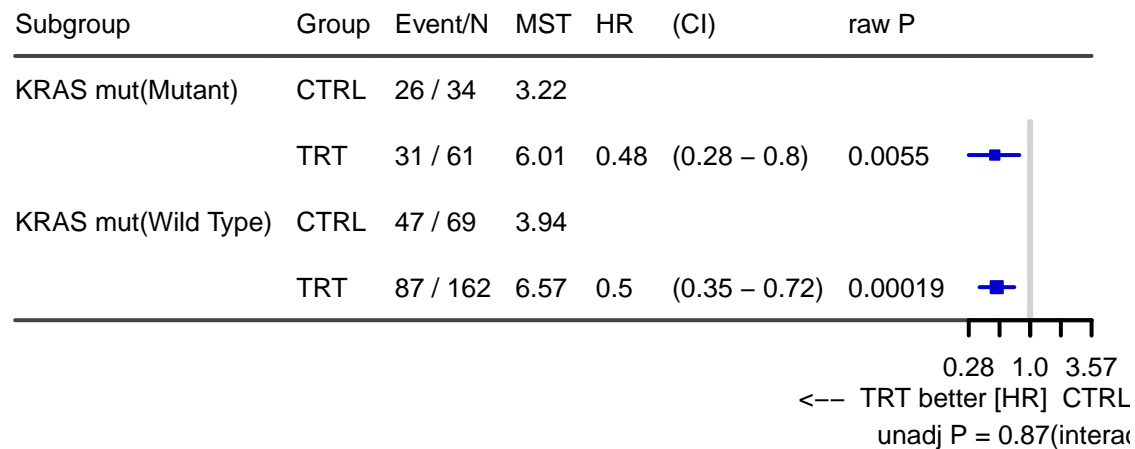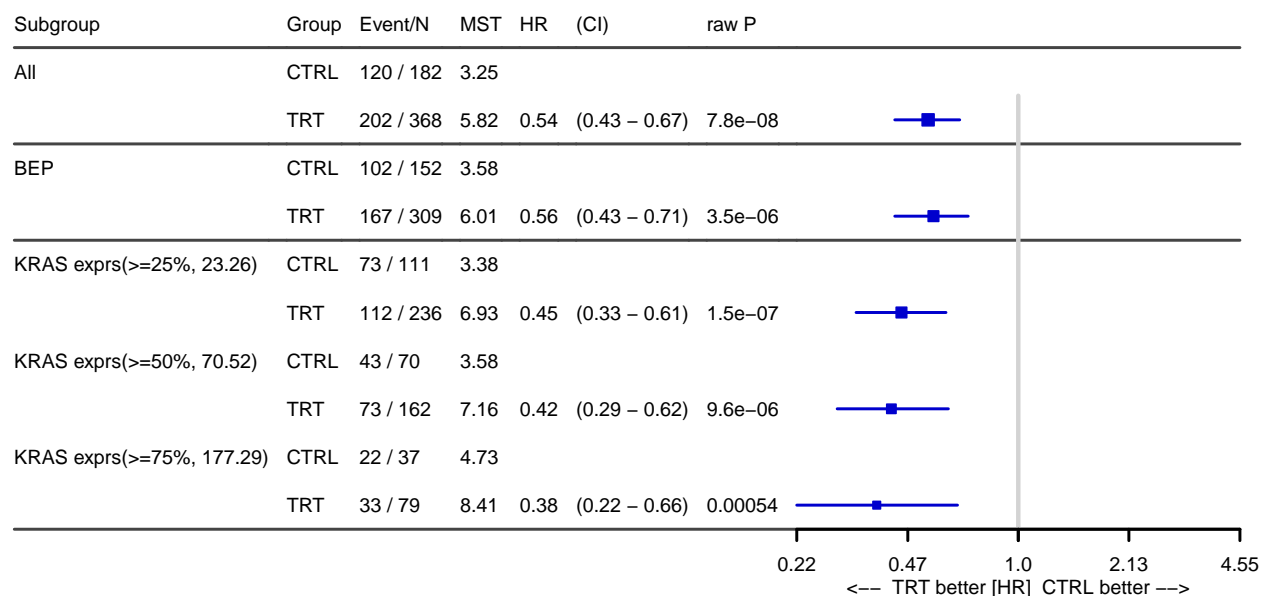
53
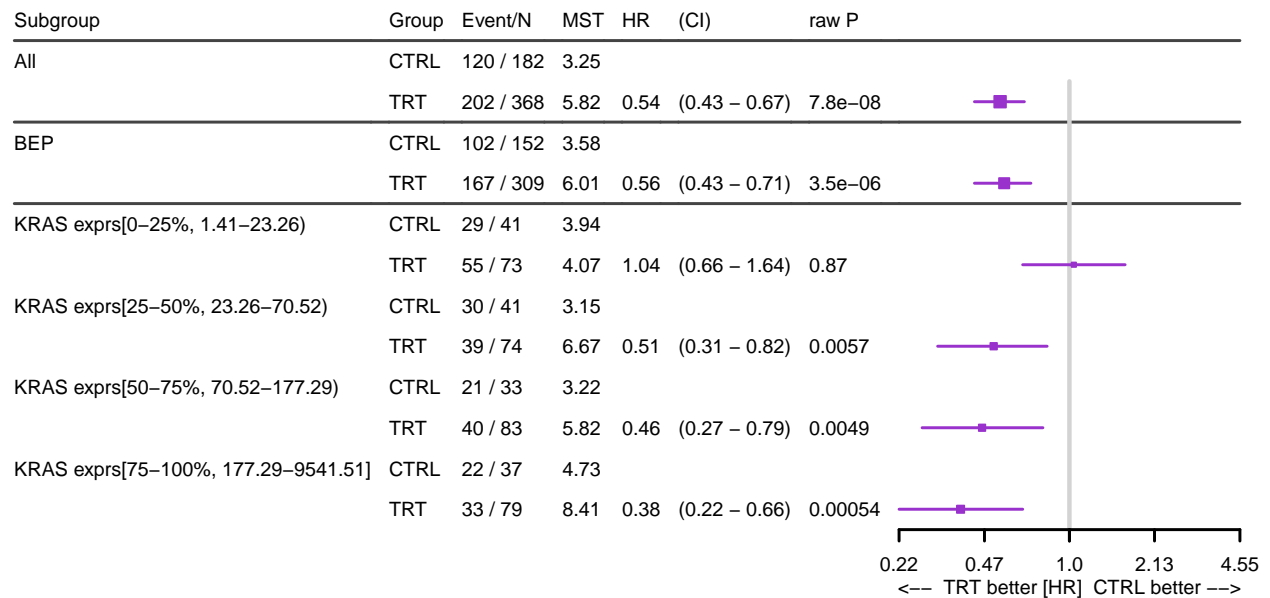
```
##  [3,] ""                                    "TRT"   "202 / 368" "5.82"
##  [4,] "BEP"                                  "CTRL"  "102 / 152" "3.58"
##  [5,] ""                                    "TRT"   "167 / 309" "6.01"
##  [6,] "KRAS exprs[0-25%, 1.41-23.26)"        "CTRL"  "29 / 41"   "3.94"
##  [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" "7.8e-08"
##  [4,] ""        ""             ""
##  [5,] "0.56" "0.43 - 0.71" "3.5e-06"
##  [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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	102 / 152	3.58			
	TRT	167 / 309	6.01	0.56	(0.43 – 0.71)	3.5e–06
KRAS exprs(>=50)	CTRL	54 / 85	3.45			
	TRT	85 / 189	7.16	0.42	(0.3 – 0.6)	1.2e–06
KRAS exprs(>=100)	CTRL	32 / 53	3.45			
	TRT	56 / 125	7.82	0.42	(0.27 – 0.65)	0.00011

```
0.27          0.52        1.0        1.92      3.7
        <-- TRT better [HR] CTRL better -->
```

```
##                                 code.v
## [1,] "Subgroup"              "Group" "Event/N"    "MST"   "HR"    "CI"
## [2,] "All"                   "CTRL"  "120 / 182" "3.25" ""      ""
## [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,] "7.8e-08"
## [4,] ""
## [5,] "3.5e-06"
## [6,] ""
## [7,] "1.2e-06"
## [8,] ""
## [9,] "0.00011"
```
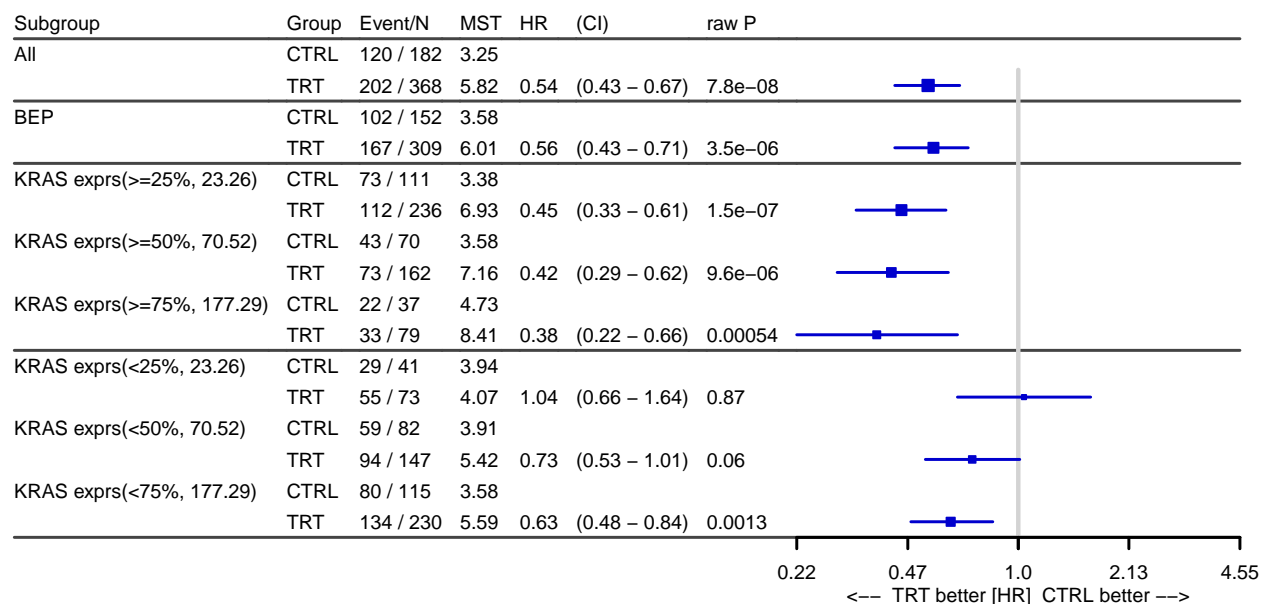
7.9 Survival outcome, 2-arm, continuous variable, adjust for covariates

```
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;

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.53	(0.42 – 0.67)	5e–08
BEP	CTRL	59 / 81	3.58			
	TRT	91 / 176	6.54	0.5	(0.36 – 0.69)	3.1e–05
KRAS exprs(>=50)	CTRL	31 / 42	3.38			
	TRT	45 / 104	8.41	0.38	(0.24 – 0.61)	5e–05
KRAS exprs(>=100)	CTRL	20 / 28	3.45			
	TRT	28 / 71	8.51	0.34	(0.19 – 0.61)	0.00034

```
          0.19        0.44        1.0        2.29        5.26
                 <-- TRT better [HR]  CTRL better -->
```

```
##                              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"  "0.38"  "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,] "5e-08"
## [4,] ""
## [5,] "3.1e-05"
## [6,] ""
## [7,] "5e-05"
## [8,] ""
```

```
## [9,] "0.00034"
```

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

```r
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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	8.4e–08
BEP	CTRL	59 / 81	3.58			
	TRT	91 / 176	6.54	0.5	(0.36 – 0.69)	3.8e–05
KRAS exprs(>=50)	CTRL	31 / 42	3.38			
	TRT	45 / 104	8.41	0.38	(0.24 – 0.61)	6.7e–05
KRAS exprs(>=100)	CTRL	20 / 28	3.45			
	TRT	28 / 71	8.51	0.34	(0.19 – 0.63)	0.00046

```
              0.19      0.44    1.0      2.29    5.26
                <–– TRT better [HR] CTRL better ––>
```
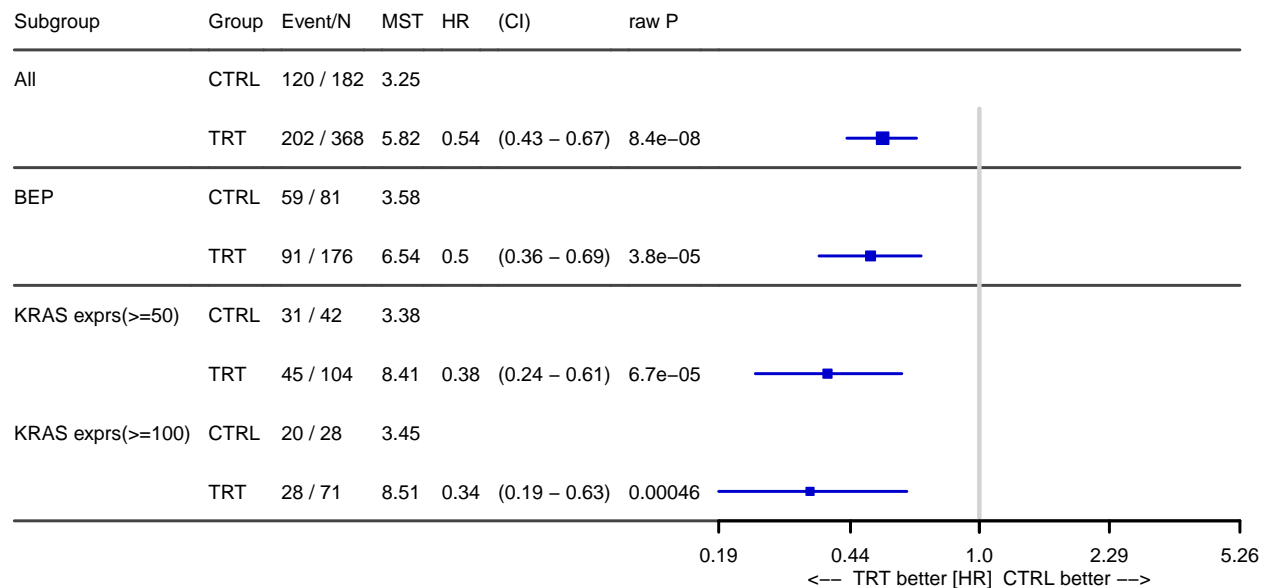
```
##                           code.v
## [1,] "Subgroup"           "Group" "Event/N"    "MST"   "HR"    "CI"
## [2,] "All"                "CTRL"  "120 / 182" "3.25" ""       ""
## [3,] ""                   "TRT"   "202 / 368" "5.82" "0.54" "0.43 - 0.67"
## [4,] "BEP"                "CTRL"  "59 / 81"   "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,] "8.4e-08"
## [4,] ""
## [5,] "3.8e-05"
## [6,] ""
## [7,] "6.7e-05"
## [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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.53	(0.42 – 0.67)	5.3e–08
BEP	CTRL	59 / 81	3.58			
	TRT	91 / 176	6.54	0.5	(0.36 – 0.69)	3.5e–05
KRAS exprs(>=50)	CTRL	31 / 42	3.38			
	TRT	45 / 104	8.41	0.39	(0.24 – 0.62)	7.8e–05
KRAS exprs(>=100)	CTRL	20 / 28	3.45			
	TRT	28 / 71	8.51	0.34	(0.19 – 0.62)	0.00039

0.19   0.44   1.0   2.29   5.26

<–– TRT better [HR] CTRL better ––>

```
##                              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,] "5.3e-08"
## [4,] ""
## [5,] "3.5e-05"
## [6,] ""
## [7,] "7.8e-05"
## [8,] ""
## [9,] "0.00039"
```

7.12 Survival outcome, 1arm

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

```r
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)	9.5e–05	
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
```
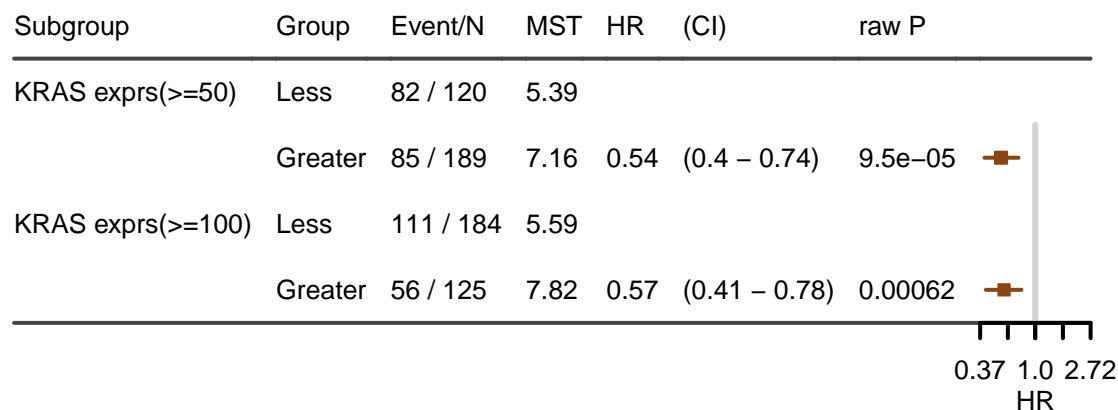
```
##                                code.v
## [1,] "Subgroup"               "Group"    "Event/N"    "MST"   "HR"    "CI"
## [2,] "KRAS exprs(>=50)"  "Less"     "82 / 120"   "5.39" ""      ""
## [3,] ""                       "Greater" "85 / 189"   "7.16" "0.54" "0.4 - 0.74"
## [4,] "KRAS exprs(>=100)" "Less"     "111 / 184" "5.59" ""      ""
## [5,] ""                       "Greater" "56 / 125"   "7.82" "0.57" "0.41 - 0.78"
##
## [1,] "raw P"
## [2,] ""
## [3,] "9.5e-05"
## [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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	TRT	202 / 368	5.82			
	CTRL	120 / 182	3.25	1.87	(1.49 – 2.34)	7.8e–08
BEP	TRT	167 / 309	6.01			
	CTRL	102 / 152	3.58	1.8	(1.4 – 2.3)	3.5e–06
KRAS exprs(>=25%, 23.26)	TRT	112 / 236	6.93			
	CTRL	73 / 111	3.38	2.23	(1.65 – 3)	1.5e–07
KRAS exprs(>=50%, 70.52)	TRT	73 / 162	7.16			
	CTRL	43 / 70	3.58	2.37	(1.62 – 3.48)	9.6e–06
KRAS exprs(>=75%, 177.29)	TRT	33 / 79	8.41			
	CTRL	22 / 37	4.73	2.64	(1.52 – 4.57)	0.00054

```
                        0.22      0.47    1.0      2.14      4.57
                        <–– CTRL better [HR]  TRT better ––>
```
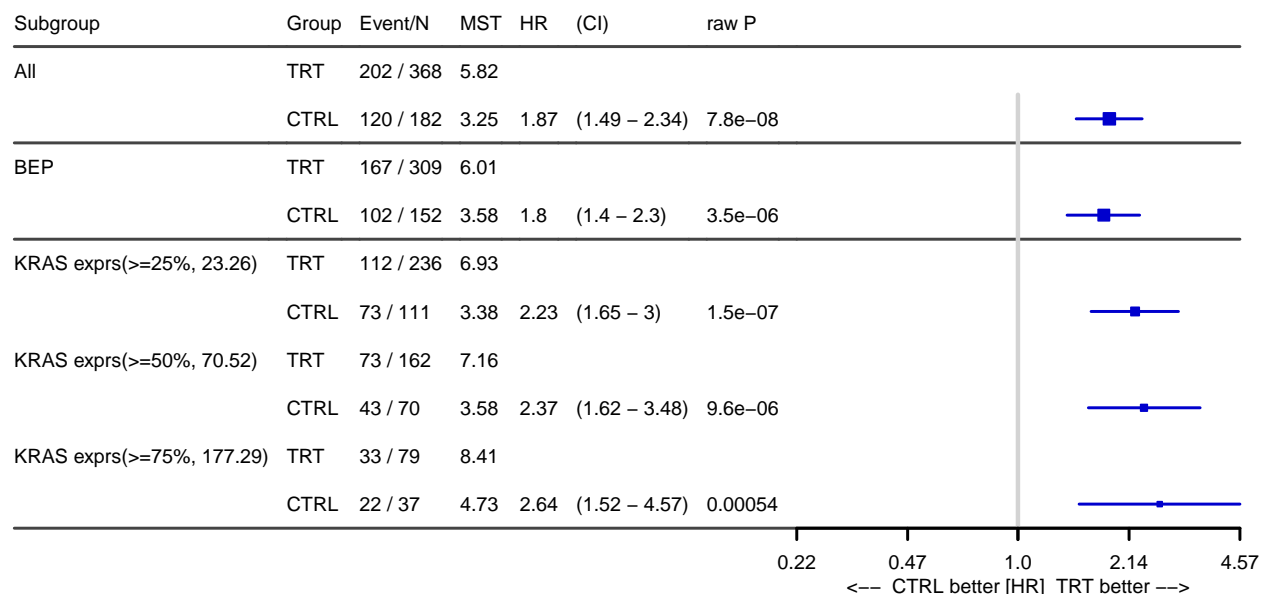
```
##                                          code.v
##  [1,] "Subgroup"                         "Group" "Event/N"    "MST"  "HR"
##  [2,] "All"                              "TRT"   "202 / 368" "5.82" ""
##  [3,] ""                                 "CTRL"  "120 / 182" "3.25" "1.87"
##  [4,] "BEP"                              "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" "7.8e-08"
##  [4,] ""             ""
##  [5,] "1.4 - 2.3"   "3.5e-06"
##  [6,] ""             ""
##  [7,] "1.65 - 3"    "1.5e-07"
##  [8,] ""             ""
##  [9,] "1.62 - 3.48" "9.6e-06"
## [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
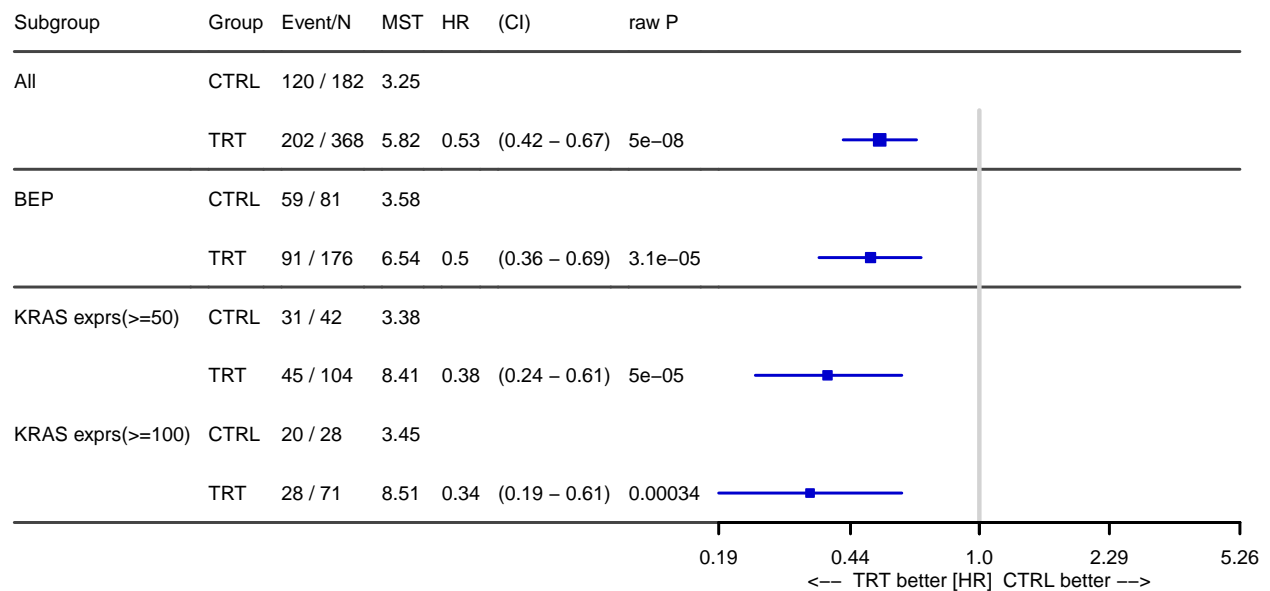
```
PlotTabForestBiomarker(data=input,
                              outcome.class="survival",
                              outcome.var=c("PFS","PFS.event"),
                              trt="Arm",
                              var="KRAS.exprs",
                              var.class="numeric", var.name="KRAS 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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
All	CTRL	120 / 182	3.25			
	TRT	202 / 368	5.82	0.54	(0.43 – 0.67)	7.8e–08
BEP	CTRL	102 / 152	3.58			
	TRT	167 / 309	6.01	0.56	(0.43 – 0.71)	3.5e–06
KRAS exprs(>=25%, 23.26)	CTRL	73 / 111	3.38			
	TRT	112 / 236	6.93	0.45	(0.33 – 0.61)	1.5e–07
KRAS exprs(>=50%, 70.52)	CTRL	43 / 70	3.58			
	TRT	73 / 162	7.16	0.42	(0.29 – 0.62)	9.6e–06
KRAS exprs(>=75%, 177.29)	CTRL	22 / 37	4.73			
	TRT	33 / 79	8.41	0.38	(0.22 – 0.66)	0.00054
CTRL:KRAS exprs(>=25%, 23.26)	Less	29 / 41	3.94			
	Greater	73 / 111	3.38	1.09	(0.7 – 1.68)	0.71
CTRL:KRAS exprs(>=50%, 70.52)	Less	59 / 82	3.91			
	Greater	43 / 70	3.58	1	(0.67 – 1.48)	1
CTRL:KRAS exprs(>=75%, 177.29)	Less	80 / 115	3.58			
	Greater	22 / 37	4.73	0.85	(0.53 – 1.37)	0.5
TRT:KRAS exprs(>=25%, 23.26)	Less	55 / 73	4.07			
	Greater	112 / 236	6.93	0.45	(0.33 – 0.63)	2e–06
TRT:KRAS exprs(>=50%, 70.52)	Less	94 / 147	5.42			
	Greater	73 / 162	7.16	0.57	(0.42 – 0.78)	0.00043
TRT:KRAS exprs(>=75%, 177.29)	Less	134 / 230	5.59			
	Greater	33 / 79	8.41	0.51	(0.35 – 0.75)	0.00061

```
            0.22   0.47   1.0   2.13   4.55
                          HR
```

```
##                                 code.v
##  [1,] "Subgroup"                "Group"    "Event/N"    "MST"    "HR"
##  [2,] "All"                     "CTRL"     "120 / 182"  "3.25"   ""
```
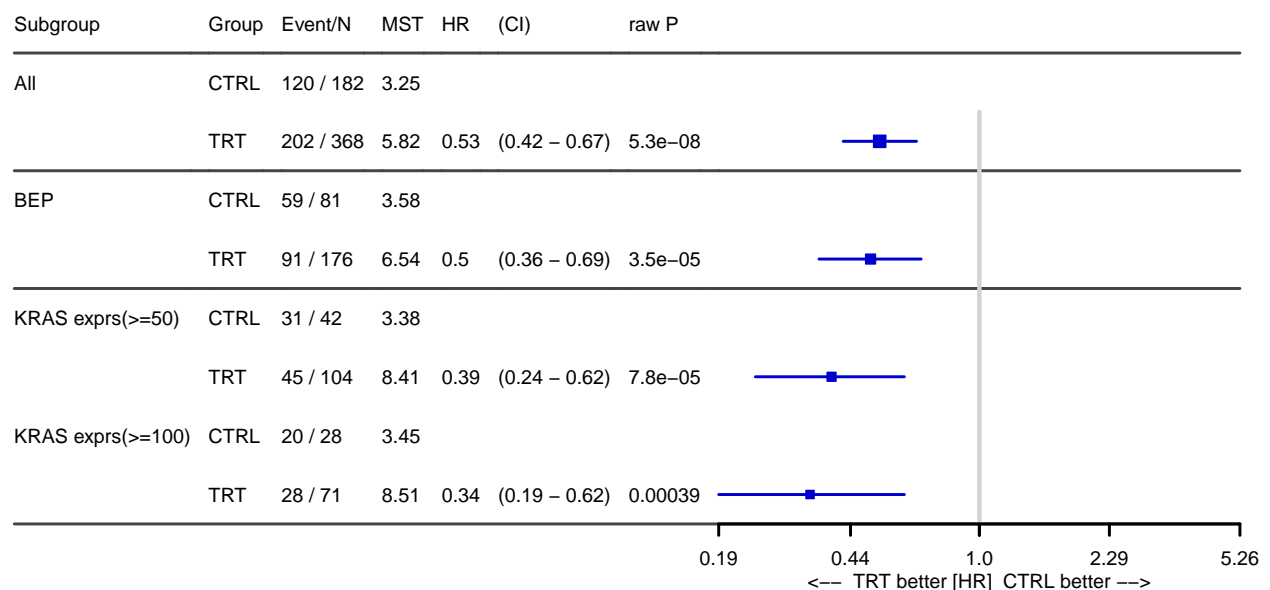
```
## [3,]  ""                                  "TRT"     "202 / 368" "5.82" "0.54"
## [4,]  "BEP"                               "CTRL"    "102 / 152" "3.58" ""
## [5,]  ""                                  "TRT"     "167 / 309" "6.01" "0.56"
## [6,]  "KRAS exprs(>=25%, 23.26)"          "CTRL"    "73 / 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"
## [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" "7.8e-08"
## [4,]  ""            ""
## [5,]  "0.43 - 0.71" "3.5e-06"
## [6,]  ""            ""
## [7,]  "0.33 - 0.61" "1.5e-07"
## [8,]  ""            ""
## [9,]  "0.29 - 0.62" "9.6e-06"
## [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" "2e-06"
## [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")
```
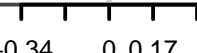
Covariate adjustment and stratification are not supported for binary outcome

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)	7e–07	
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 0.17
                <−−  CTRL better [deltaRR]  TRT
                        * Unadj P = 0.77 (interact
```

```
##                              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"  "7e-07"
## [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

Subgroup	Group	nRsp/N	Rsp Rate	deltaRR	CI	raw P	Forest plot	
							CTRL better	TRT better
All	CTRL	14 / 182	0.08					
	TRT	96 / 368	0.26	0.18	0.12 – 0.25	7e–07		
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		

* Unadj P = 0.77 (interaction)

Unadjusted, unstratified analysis

−0.34 −0.17 0 0.17 0.34

```
##                                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" "7e-07"
## [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
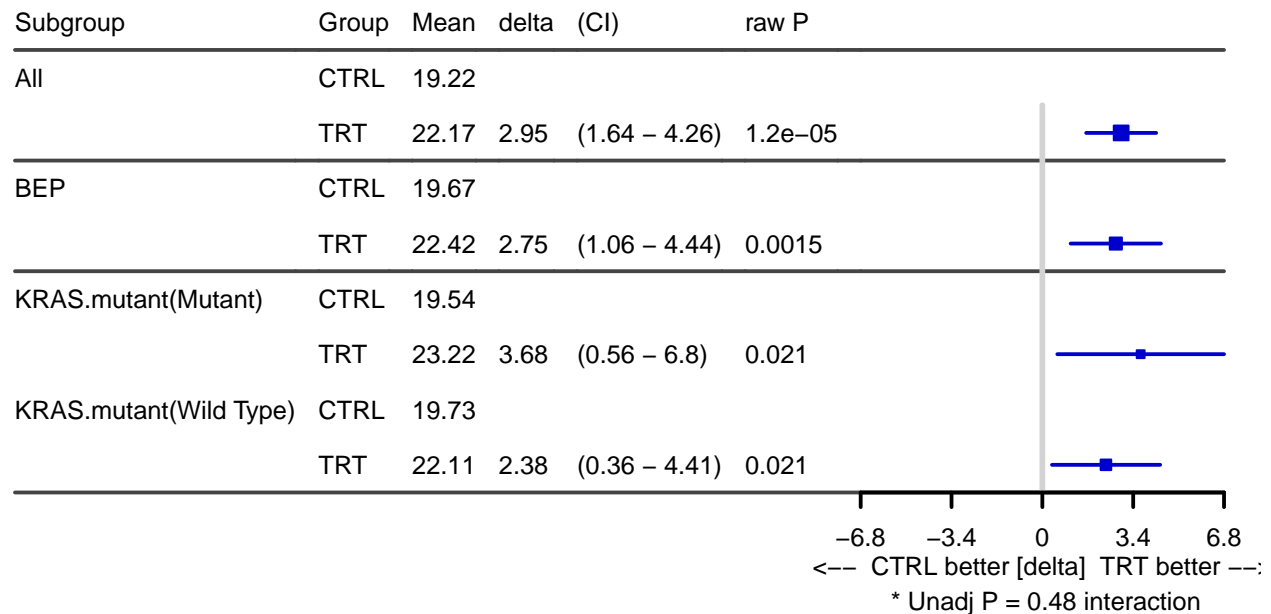
Subgroup	Group	Mean	delta	(CI)	raw P	
All	CTRL	19.22				
	TRT	22.17	2.95	(1.64 – 4.26)	1.2e–05	
BEP	CTRL	19.67				
	TRT	22.42	2.75	(1.06 – 4.44)	0.0015	
KRAS.mutant(Mutant)	CTRL	19.54				
	TRT	23.22	3.68	(0.56 – 6.8)	0.021	
KRAS.mutant(Wild Type)	CTRL	19.73				
	TRT	22.11	2.38	(0.36 – 4.41)	0.021	

```
              −6.8    −3.4     0     3.4     6.8
         <−−  CTRL better [delta]  TRT better −−:
                  * Unadj P = 0.48 interaction
```

```
##                          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,] "1.2e-05"
## [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

Subgroup	Group	Mean	delta	CI	raw P	Forest plot	
						CTRL better	TRT better
All	CTRL	19.22					
	TRT	22.17	2.95	1.64 – 4.26	1.2e−05		
BEP	CTRL	19.67					
	TRT	22.42	2.75	1.06 – 4.44	0.0015		
KRAS.mutant(Mutant)	CTRL	19.54					
	TRT	23.22	3.68	0.56 – 6.8	0.021		
KRAS.mutant(Wild Type)	CTRL	19.73					
	TRT	22.11	2.38	0.36 – 4.41	0.021		

* Unadj P = 0.48 interaction

Unadjusted, unstratified analysis

−6.8   −3.4   0   3.4   6.8

```
##                                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"
```
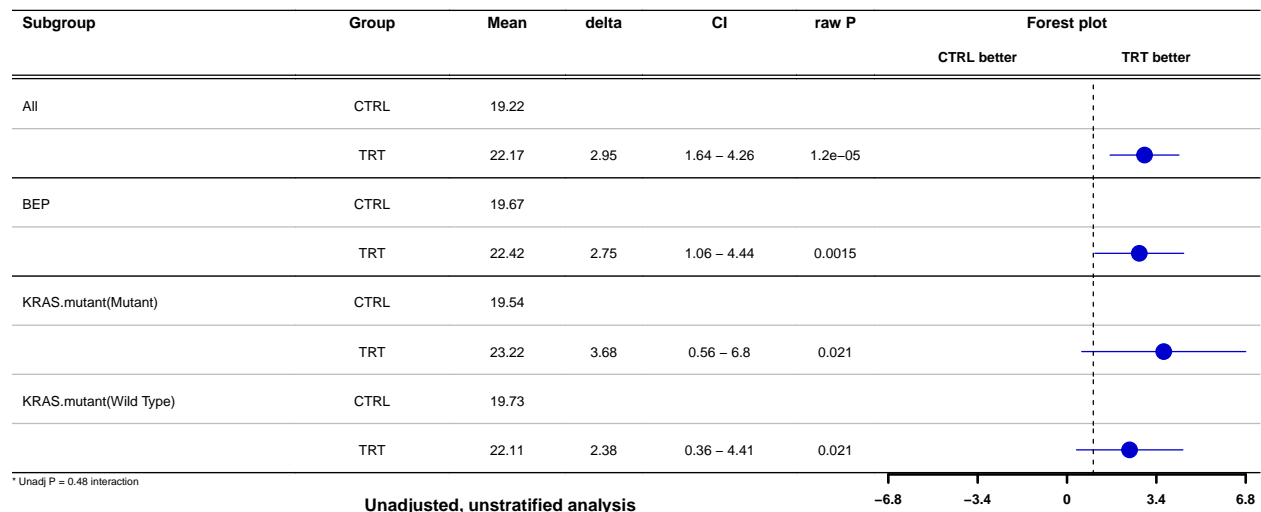
```
## [8,] "KRAS.mutant(Wild Type)" "CTRL" "19.73" ""     ""
## [9,] ""                       "TRT"  "22.11" "2.38" "0.36 - 4.41"
##
## [1,] "raw P"
## [2,] ""
## [3,] "1.2e-05"
## [4,] ""
## [5,] "0.0015"
## [6,] ""
## [7,] "0.021"
## [8,] ""
## [9,] "0.021"
```

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
ITT Sex(F)	CTRL	57 / 89	3.38			
	TRT	105 / 184	5.72	0.54	(0.39 – 0.74)	0.00018
BEP Sex(F)	CTRL	28 / 39	4.14			
	TRT	52 / 90	5.49	0.58	(0.36 – 0.92)	0.021
ITT Sex(M)	CTRL	63 / 93	3.22			
	TRT	97 / 184	6.54	0.54	(0.39 – 0.74)	0.00012
BEP Sex(M)	CTRL	31 / 42	3.02			
	TRT	39 / 86	6.8	0.42	(0.26 – 0.68)	0.00043
ITT Age(>=50%, 53)	CTRL	56 / 80	3.06			
	TRT	120 / 207	5.59	0.56	(0.41 – 0.77)	0.00035
BEP Age(>=50%, 54)	CTRL	26 / 36	3.38			
	TRT	53 / 93	5.72	0.63	(0.39 – 1.01)	0.053
ITT Age(<50%, 53)	CTRL	64 / 102	3.94			
	TRT	82 / 161	6.8	0.48	(0.35 – 0.67)	1.9e−05
BEP Age(<50%, 54)	CTRL	33 / 45	3.91			
	TRT	38 / 83	6.8	0.37	(0.23 – 0.6)	4.8e−05

0   0.5   1

<−− TRT better [HR] CTRL better −−>

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
Mutant Age(>=50%, 54)	CTRL	11 / 14	3.58			
	TRT	19 / 36	6.01	0.59	(0.28 – 1.26)	0.17
Wild Type Age(>=50%, 53)	CTRL	22 / 32	2.96			
	TRT	52 / 87	5.72	0.53	(0.32 – 0.88)	0.013
Mutant Age(<50%, 54)	CTRL	15 / 20	3.14			
	TRT	12 / 25	7.13	0.39	(0.18 – 0.84)	0.017
Wild Type Age(<50%, 53)	CTRL	25 / 37	4.47			
	TRT	35 / 75	6.8	0.46	(0.27 – 0.77)	0.0033

0   0.5   1   1.5

<-- TRT better [HR] CTRL better -->

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
ITT Sex(F)	CTRL	57 / 89	3.38			
	TRT	105 / 184	5.72	0.54	(0.39 – 0.74)	0.00018
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
ITT Sex(M)	CTRL	63 / 93	3.22			
	TRT	97 / 184	6.54	0.54	(0.39 – 0.74)	0.00012
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
ITT Age(>=50%, 53)	CTRL	56 / 80	3.06			
	TRT	120 / 207	5.59	0.56	(0.41 – 0.77)	0.00035
Mutant Age(>=50%, 54)	CTRL	11 / 14	3.58			
	TRT	19 / 36	6.01	0.59	(0.28 – 1.26)	0.17
Wild Type Age(>=50%, 53)	CTRL	22 / 32	2.96			
	TRT	52 / 87	5.72	0.53	(0.32 – 0.88)	0.013
ITT Age(<50%, 53)	CTRL	64 / 102	3.94			
	TRT	82 / 161	6.8	0.48	(0.35 – 0.67)	1.9e–05
Mutant Age(<50%, 54)	CTRL	15 / 20	3.14			
	TRT	12 / 25	7.13	0.39	(0.18 – 0.84)	0.017
Wild Type Age(<50%, 53)	CTRL	25 / 37	4.47			
	TRT	35 / 75	6.8	0.46	(0.27 – 0.77)	0.0033

```
0        0.5        1        1.5
<–– TRT better [ HR ]  CTRL better –
```

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
ITT Sex(F)	CTRL	57 / 89	3.38			
	TRT	105 / 184	5.72	0.54	(0.39 – 0.74)	0.00018
BEP Sex(F)	CTRL	28 / 39	4.14			
	TRT	52 / 90	5.49	0.58	(0.36 – 0.92)	0.021
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
ITT Sex(M)	CTRL	63 / 93	3.22			
	TRT	97 / 184	6.54	0.54	(0.39 – 0.74)	0.00012
BEP Sex(M)	CTRL	31 / 42	3.02			
	TRT	39 / 86	6.8	0.42	(0.26 – 0.68)	0.00043
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
ITT Age(>=50%, 53)	CTRL	56 / 80	3.06			
	TRT	120 / 207	5.59	0.56	(0.41 – 0.77)	0.00035
BEP Age(>=50%, 54)	CTRL	26 / 36	3.38			
	TRT	53 / 93	5.72	0.63	(0.39 – 1.01)	0.053
Mutant Age(>=50%, 54)	CTRL	11 / 14	3.58			
	TRT	19 / 36	6.01	0.59	(0.28 – 1.26)	0.17
Wild Type Age(>=50%, 53)	CTRL	22 / 32	2.96			
	TRT	52 / 87	5.72	0.53	(0.32 – 0.88)	0.013
ITT Age(<50%, 53)	CTRL	64 / 102	3.94			
	TRT	82 / 161	6.8	0.48	(0.35 – 0.67)	1.9e−05
BEP Age(<50%, 54)	CTRL	33 / 45	3.91			
	TRT	38 / 83	6.8	0.37	(0.23 – 0.6)	4.8e−05
Mutant Age(<50%, 54)	CTRL	15 / 20	3.14			
	TRT	12 / 25	7.13	0.39	(0.18 – 0.84)	0.017
Wild Type Age(<50%, 53)	CTRL	25 / 37	4.47			
	TRT	35 / 75	6.8	0.46	(0.27 – 0.77)	0.0033

0   0.5   1   1.5

<−− TRT better [HR] CTRL better −

If bep column is not defined, the program will take the non NA entries in subgroups column as BEP
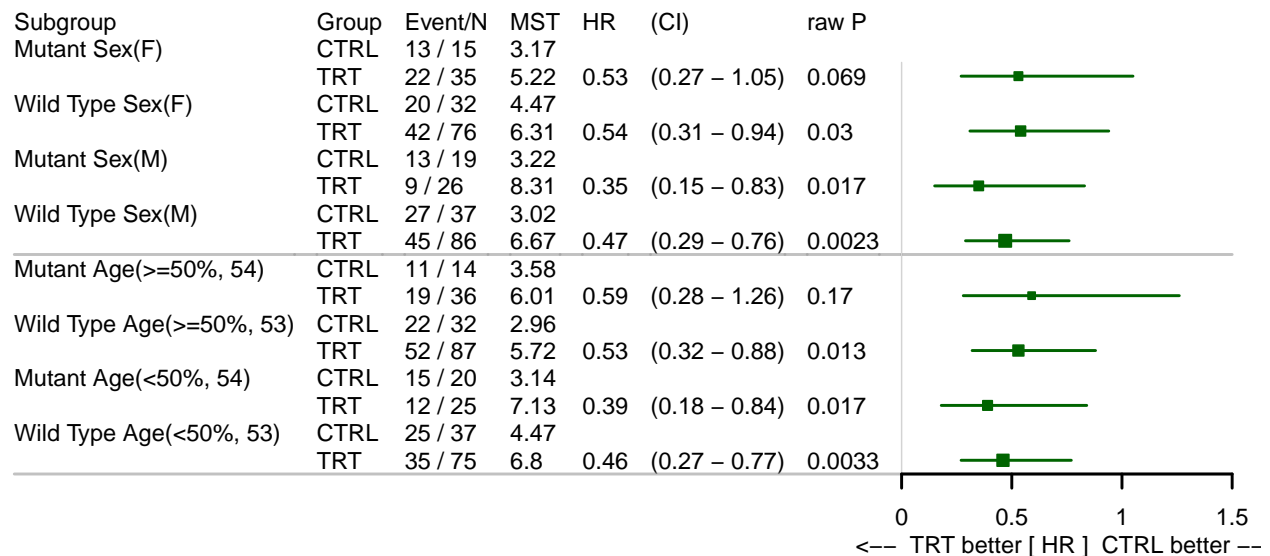
```
PlotTabForestMulti(data=input,
                                 outcome.class="survival",
                                 outcome.var=c("PFS","PFS.event"),
                                 trt="Arm",
                                 var=c("Sex","Age"), compare.bep.itt=FALSE,
                    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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
ITT Sex(F)	CTRL	57 / 89	3.38			
	TRT	105 / 184	5.72	0.54	(0.39 – 0.74)	0.00018
BEP Sex(F)	CTRL	33 / 47	4.11			
	TRT	64 / 111	5.59	0.53	(0.35 – 0.81)	0.0037
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
ITT Sex(M)	CTRL	63 / 93	3.22			
	TRT	97 / 184	6.54	0.54	(0.39 – 0.74)	0.00012
BEP Sex(M)	CTRL	40 / 56	3.06			
	TRT	54 / 112	6.8	0.46	(0.3 – 0.7)	0.00024
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
ITT Age(>=50%, 53)	CTRL	56 / 80	3.06			
	TRT	120 / 207	5.59	0.56	(0.41 – 0.77)	0.00035
BEP Age(>=50%, 53)	CTRL	34 / 47	3.02			
	TRT	71 / 123	6.01	0.52	(0.34 – 0.79)	0.0019
Mutant Age(>=50%, 54)	CTRL	11 / 14	3.58			
	TRT	19 / 36	6.01	0.59	(0.28 – 1.26)	0.17
Wild Type Age(>=50%, 53)	CTRL	22 / 32	2.96			
	TRT	52 / 87	5.72	0.53	(0.32 – 0.88)	0.013
ITT Age(<50%, 53)	CTRL	64 / 102	3.94			
	TRT	82 / 161	6.8	0.48	(0.35 – 0.67)	1.9e−05
BEP Age(<50%, 53)	CTRL	39 / 56	4.11			
	TRT	47 / 100	6.8	0.44	(0.29 – 0.67)	0.00017
Mutant Age(<50%, 54)	CTRL	15 / 20	3.14			
	TRT	12 / 25	7.13	0.39	(0.18 – 0.84)	0.017
Wild Type Age(<50%, 53)	CTRL	25 / 37	4.47			
	TRT	35 / 75	6.8	0.46	(0.27 – 0.77)	0.0033

0   0.5   1   1.5

<−− TRT better [HR] CTRL better −

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
                 )
```
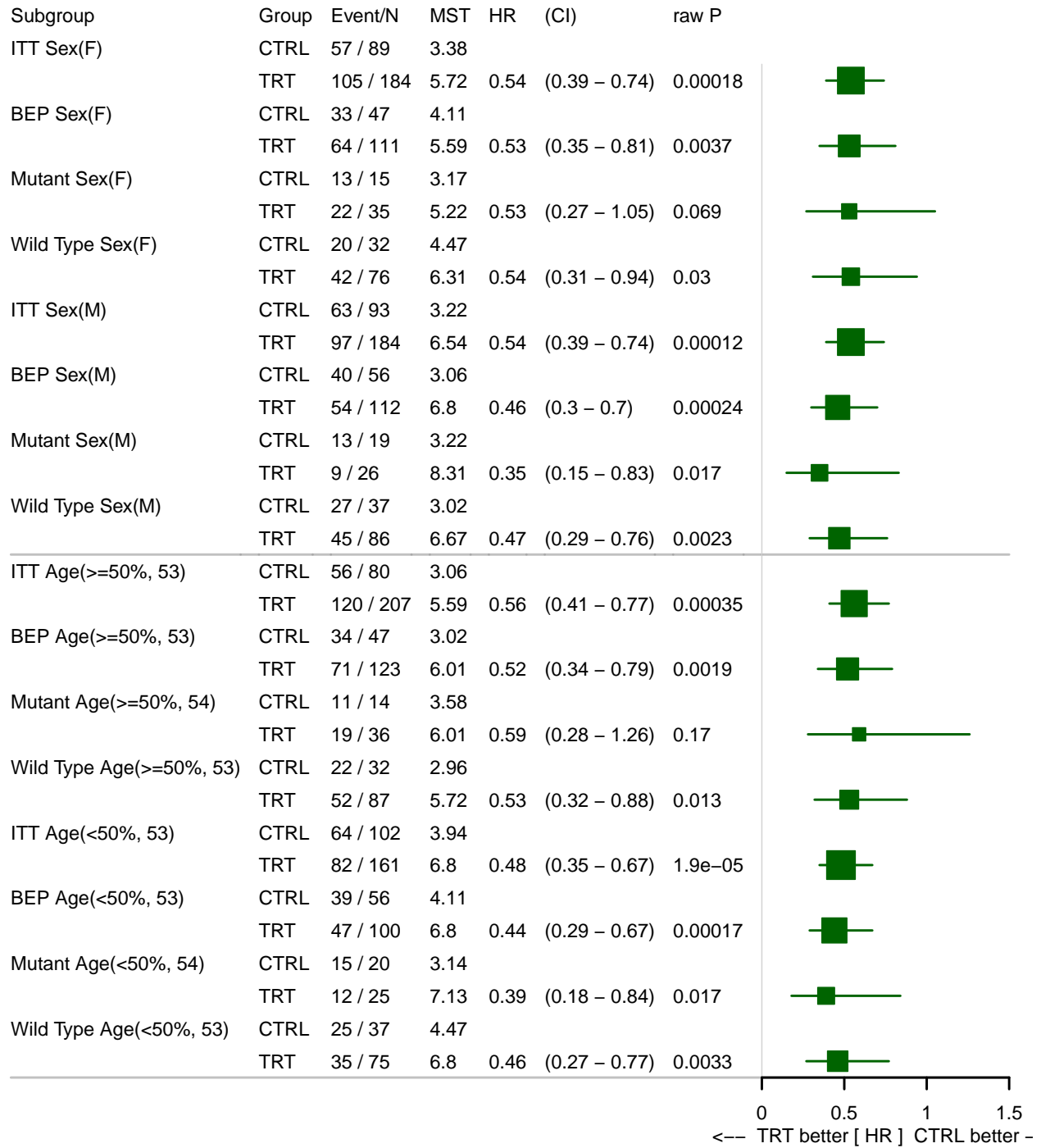
Within arm, Compare BEP vs. All

PFS

Unadjusted, unstratified analysis

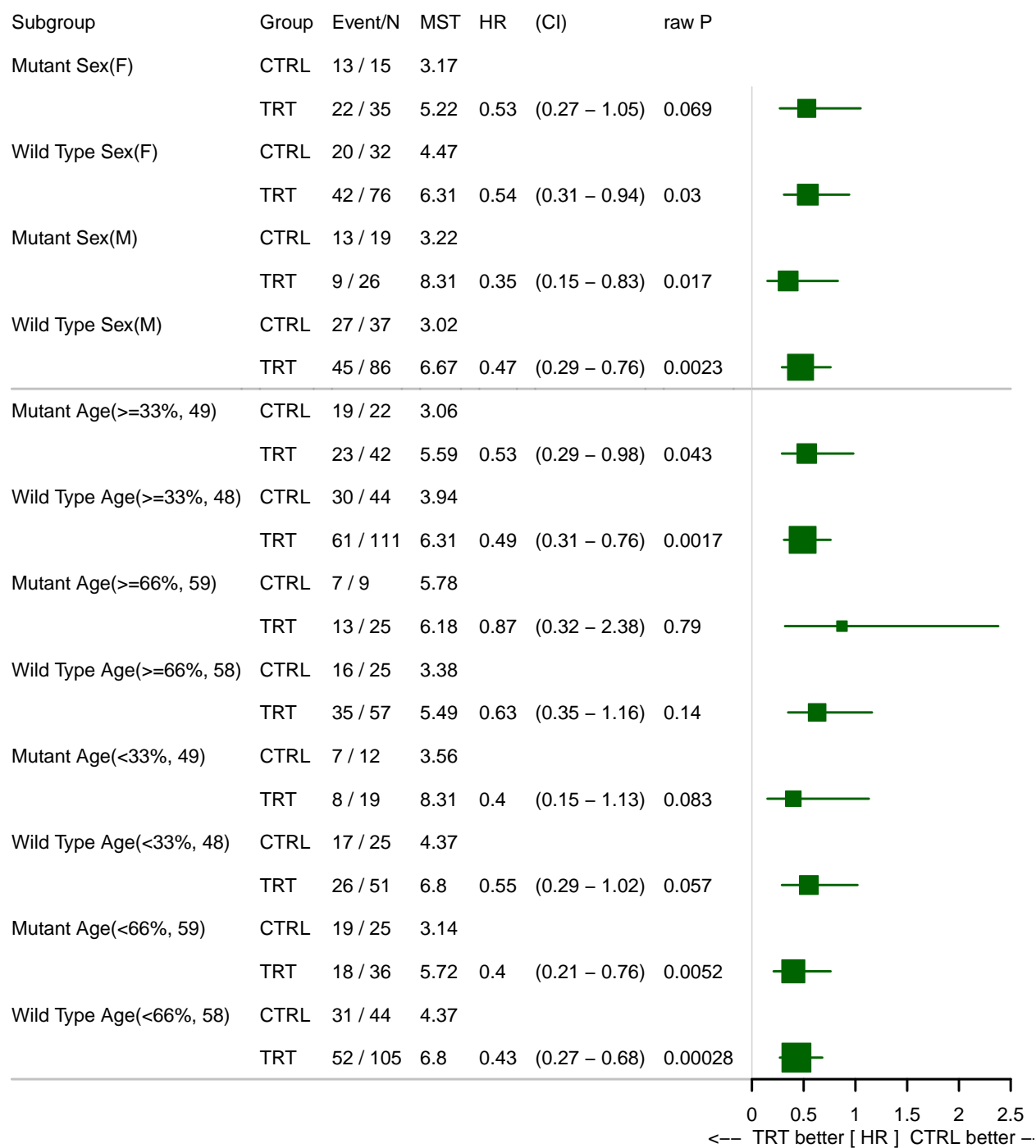| Subgroup	Group	Event/N	MST	HR	(CI)	raw P
ITT Sex(F)	No	97 / 184	6.54			
	Yes	105 / 184	5.72	1.1	(0.84 – 1.46)	0.48
BEP Sex(F)	No	39 / 86	6.8			
	Yes	52 / 90	5.49	1.41	(0.93 – 2.14)	0.11
ITT Sex(M)	No	105 / 184	5.72			
	Yes	97 / 184	6.54	0.91	(0.69 – 1.19)	0.48
BEP Sex(M)	No	52 / 90	5.49			
	Yes	39 / 86	6.8	0.71	(0.47 – 1.08)	0.11
ITT Age(>=50%, 54)	Less	91 / 177	6.8			
	Greater	111 / 191	5.59	1.3	(0.99 – 1.72)	0.063
BEP Age(>=50%, 54)	Less	38 / 83	6.8			
	Greater	53 / 93	5.72	1.48	(0.97 – 2.25)	0.068
ITT Age(<50%, 54)	Greater	111 / 191	5.59			
	Less	91 / 177	6.8	0.77	(0.58 – 1.01)	0.063
BEP Age(<50%, 54)	Greater	53 / 93	5.72			
	Less	38 / 83	6.8	0.68	(0.44 – 1.03)	0.068

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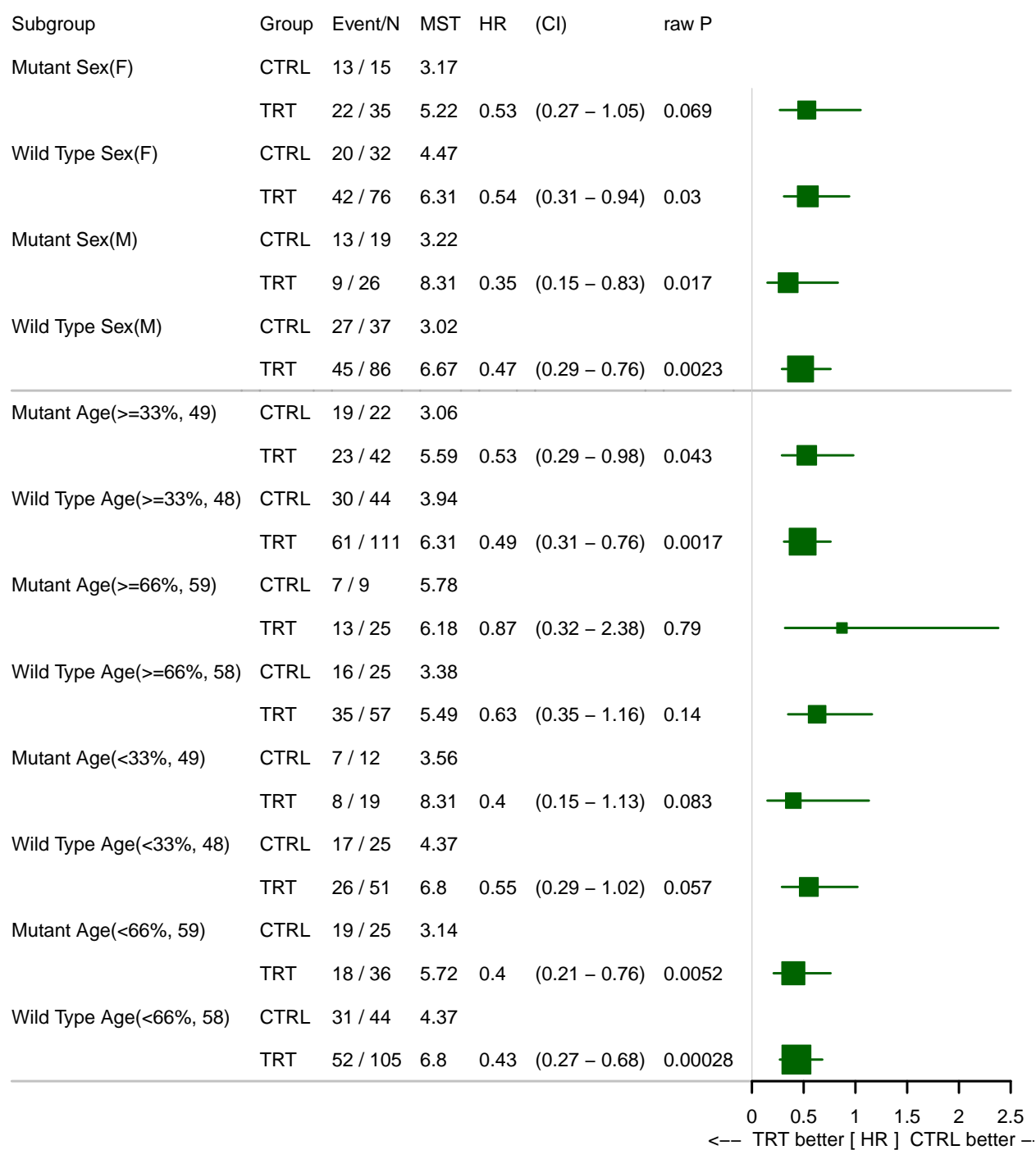
Across arm, Compare KRAS.mutant subgroup
PFS
Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
Mutant Age(>=33%, 49)	CTRL	19 / 22	3.06			
	TRT	23 / 42	5.59	0.53	(0.29 – 0.98)	0.043
Wild Type Age(>=33%, 48)	CTRL	30 / 44	3.94			
	TRT	61 / 111	6.31	0.49	(0.31 – 0.76)	0.0017
Mutant Age(>=66%, 59)	CTRL	7 / 9	5.78			
	TRT	13 / 25	6.18	0.87	(0.32 – 2.38)	0.79
Wild Type Age(>=66%, 58)	CTRL	16 / 25	3.38			
	TRT	35 / 57	5.49	0.63	(0.35 – 1.16)	0.14
Mutant Age(<33%, 49)	CTRL	7 / 12	3.56			
	TRT	8 / 19	8.31	0.4	(0.15 – 1.13)	0.083
Wild Type Age(<33%, 48)	CTRL	17 / 25	4.37			
	TRT	26 / 51	6.8	0.55	(0.29 – 1.02)	0.057
Mutant Age(<66%, 59)	CTRL	19 / 25	3.14			
	TRT	18 / 36	5.72	0.4	(0.21 – 0.76)	0.0052
Wild Type Age(<66%, 58)	CTRL	31 / 44	4.37			
	TRT	52 / 105	6.8	0.43	(0.27 – 0.68)	0.00028

0   0.5   1   1.5   2   2.5

<−− TRT better [HR] CTRL better −

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.itt=FALSE,
                  compare.subgroup=TRUE, subgroup="KRAS.mutant"
                  )
```
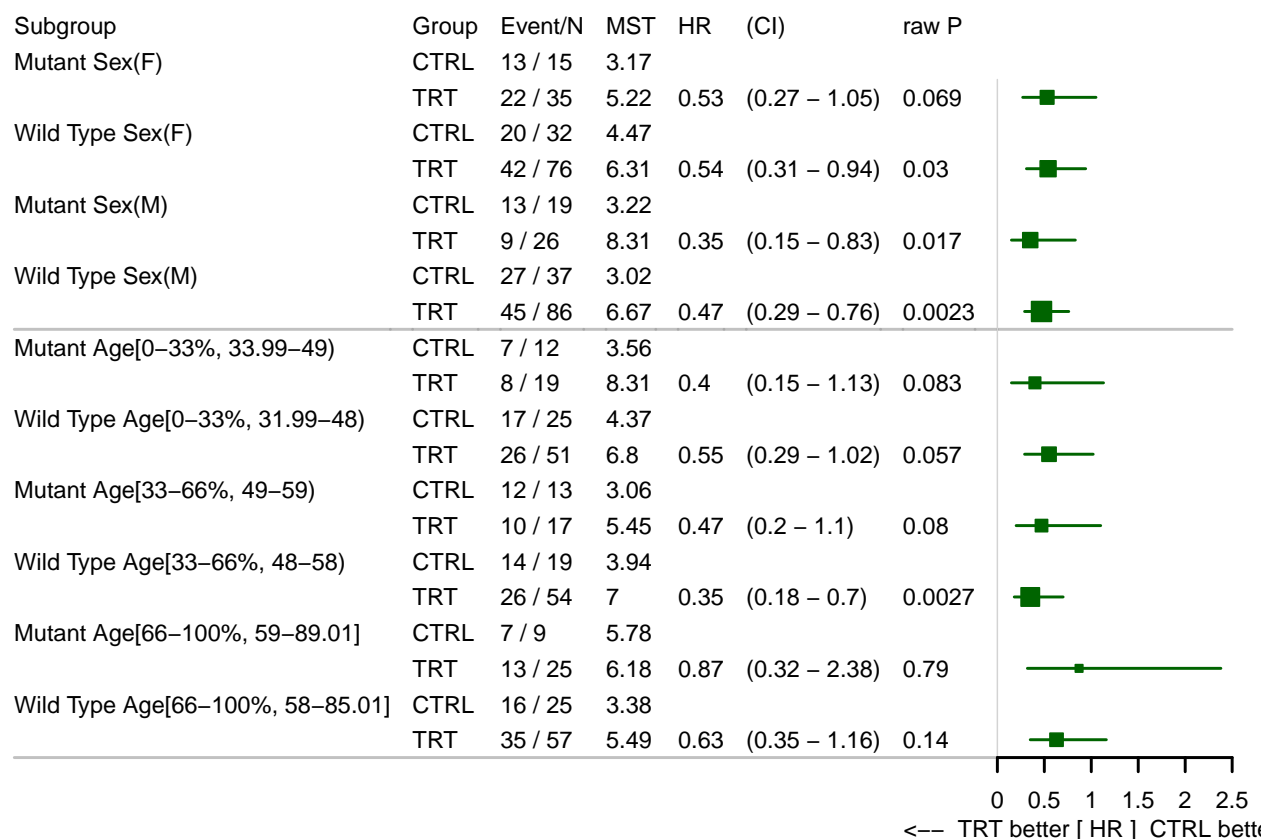
Across arm, Compare KRAS.mutant subgroup
PFS
Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
Mutant Age(>=33%, 49)	CTRL	19 / 22	3.06			
	TRT	23 / 42	5.59	0.53	(0.29 – 0.98)	0.043
Wild Type Age(>=33%, 48)	CTRL	30 / 44	3.94			
	TRT	61 / 111	6.31	0.49	(0.31 – 0.76)	0.0017
Mutant Age(>=66%, 59)	CTRL	7 / 9	5.78			
	TRT	13 / 25	6.18	0.87	(0.32 – 2.38)	0.79
Wild Type Age(>=66%, 58)	CTRL	16 / 25	3.38			
	TRT	35 / 57	5.49	0.63	(0.35 – 1.16)	0.14
Mutant Age(<33%, 49)	CTRL	7 / 12	3.56			
	TRT	8 / 19	8.31	0.4	(0.15 – 1.13)	0.083
Wild Type Age(<33%, 48)	CTRL	17 / 25	4.37			
	TRT	26 / 51	6.8	0.55	(0.29 – 1.02)	0.057
Mutant Age(<66%, 59)	CTRL	19 / 25	3.14			
	TRT	18 / 36	5.72	0.4	(0.21 – 0.76)	0.0052
Wild Type Age(<66%, 58)	CTRL	31 / 44	4.37			
	TRT	52 / 105	6.8	0.43	(0.27 – 0.68)	0.00028

0   0.5   1   1.5   2   2.5

<-- TRT better [HR] CTRL better --

8.8 2-arm, compare subgroups defined by biomarker, multiple cutoffs for continuous biomarker, calculate within bin statistics
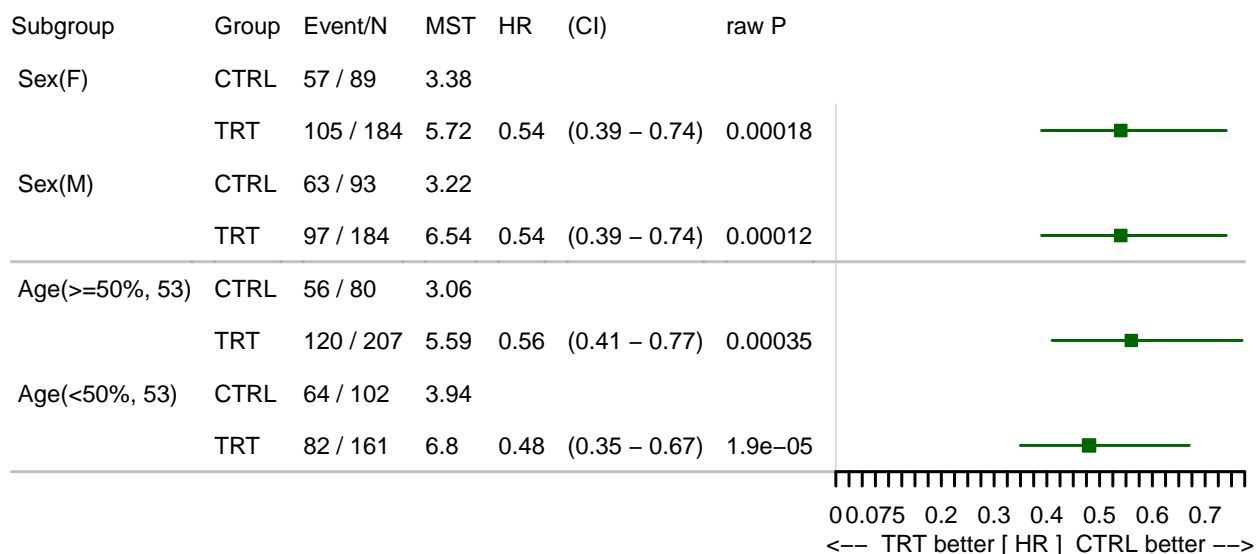
```
PlotTabForestMulti(data=input,
                          outcome.class="survival",
                          outcome.var=c("PFS","PFS.event"),
                          trt="Arm", percentile.cutoff=c(.33,.66),within.bin=TRUE,
                          var=c("Sex","Age"),
                  bep="BEP",bep.indicator=1, compare.bep.itt=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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
Mutant Sex(F)	CTRL	13 / 15	3.17			
	TRT	22 / 35	5.22	0.53	(0.27 – 1.05)	0.069
Wild Type Sex(F)	CTRL	20 / 32	4.47			
	TRT	42 / 76	6.31	0.54	(0.31 – 0.94)	0.03
Mutant Sex(M)	CTRL	13 / 19	3.22			
	TRT	9 / 26	8.31	0.35	(0.15 – 0.83)	0.017
Wild Type Sex(M)	CTRL	27 / 37	3.02			
	TRT	45 / 86	6.67	0.47	(0.29 – 0.76)	0.0023
Mutant Age[0–33%, 33.99–49)	CTRL	7 / 12	3.56			
	TRT	8 / 19	8.31	0.4	(0.15 – 1.13)	0.083
Wild Type Age[0–33%, 31.99–48)	CTRL	17 / 25	4.37			
	TRT	26 / 51	6.8	0.55	(0.29 – 1.02)	0.057
Mutant Age[33–66%, 49–59)	CTRL	12 / 13	3.06			
	TRT	10 / 17	5.45	0.47	(0.2 – 1.1)	0.08
Wild Type Age[33–66%, 48–58)	CTRL	14 / 19	3.94			
	TRT	26 / 54	7	0.35	(0.18 – 0.7)	0.0027
Mutant Age[66–100%, 59–89.01]	CTRL	7 / 9	5.78			
	TRT	13 / 25	6.18	0.87	(0.32 – 2.38)	0.79
Wild Type Age[66–100%, 58–85.01]	CTRL	16 / 25	3.38			
	TRT	35 / 57	5.49	0.63	(0.35 – 1.16)	0.14

0   0.5   1   1.5   2   2.5

<–– TRT better [HR] CTRL better

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

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
Sex(F)	CTRL	57 / 89	3.38			
	TRT	105 / 184	5.72	0.54	(0.39 – 0.74)	0.00018
Sex(M)	CTRL	63 / 93	3.22			
	TRT	97 / 184	6.54	0.54	(0.39 – 0.74)	0.00012
Age(>=50%, 53)	CTRL	56 / 80	3.06			
	TRT	120 / 207	5.59	0.56	(0.41 – 0.77)	0.00035
Age(<50%, 53)	CTRL	64 / 102	3.94			
	TRT	82 / 161	6.8	0.48	(0.35 – 0.67)	1.9e–05

00.075 0.2 0.3 0.4 0.5 0.6 0.7
<–– TRT better [HR] CTRL better ––>

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
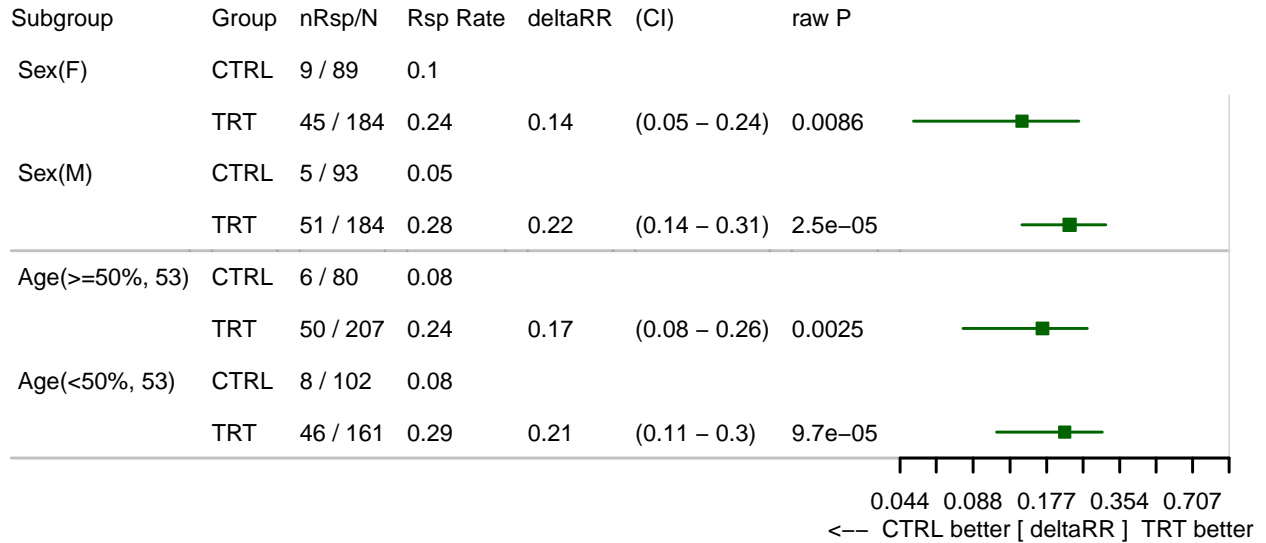
Subgroup	Group	nRsp/N	Rsp Rate	deltaRR	(CI)	raw P	
Sex(F)	CTRL	9 / 89	0.1				
	TRT	45 / 184	0.24	0.14	(0.05 – 0.24)	0.0086	
Sex(M)	CTRL	5 / 93	0.05				
	TRT	51 / 184	0.28	0.22	(0.14 – 0.31)	2.5e–05	
Age(>=50%, 53)	CTRL	6 / 80	0.08				
	TRT	50 / 207	0.24	0.17	(0.08 – 0.26)	0.0025	
Age(<50%, 53)	CTRL	8 / 102	0.08				
	TRT	46 / 161	0.29	0.21	(0.11 – 0.3)	9.7e–05	

```
0.044 0.088 0.177 0.354 0.707
<−−  CTRL better [ deltaRR ]  TRT better
```

```
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

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

Across arm
Response

Subgroup	Group	nRsp/N	Rsp Rate	deltaRR	CI	raw P	Forest plot		
							TRT better		CTRL better
Sex(F)	CTRL	9 / 89	0.1						
	TRT	45 / 184	0.24	0.14	0.05 – 0.24	0.0086			
Sex(M)	CTRL	5 / 93	0.05						
	TRT	51 / 184	0.28	0.22	0.14 – 0.31	2.5e–05			
Age(>=50%, 53)	CTRL	6 / 80	0.08						
	TRT	50 / 207	0.24	0.17	0.08 – 0.26	0.0025			
Age(<50%, 53)	CTRL	8 / 102	0.08						
	TRT	46 / 161	0.29	0.21	0.11 – 0.3	9.7e–05			

Unadjusted, unstratified analysis

0.1   0.2   0.3
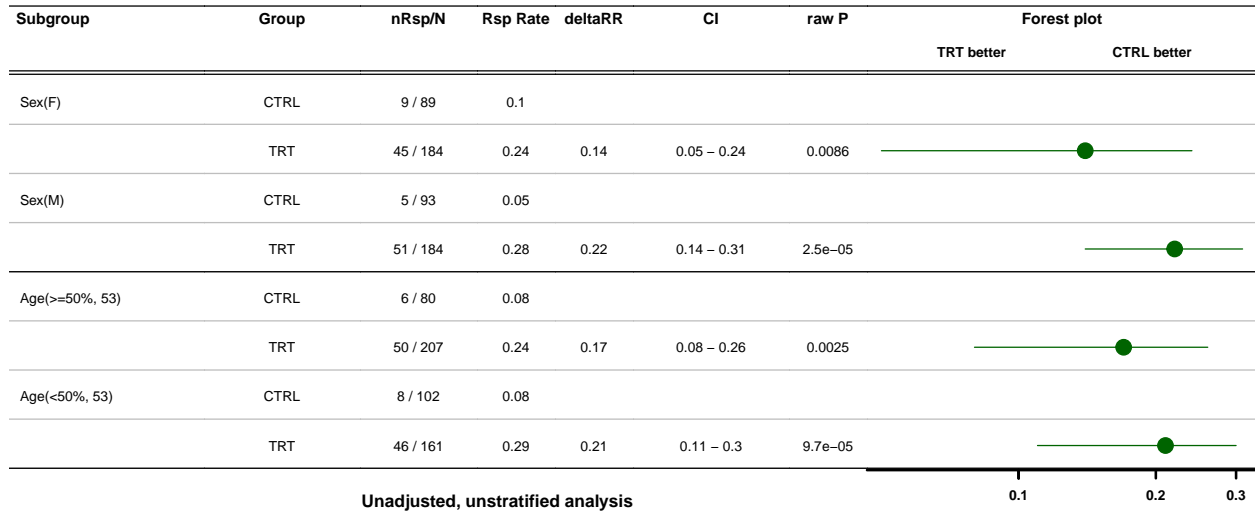
8.11   Continuous endpoint

```
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
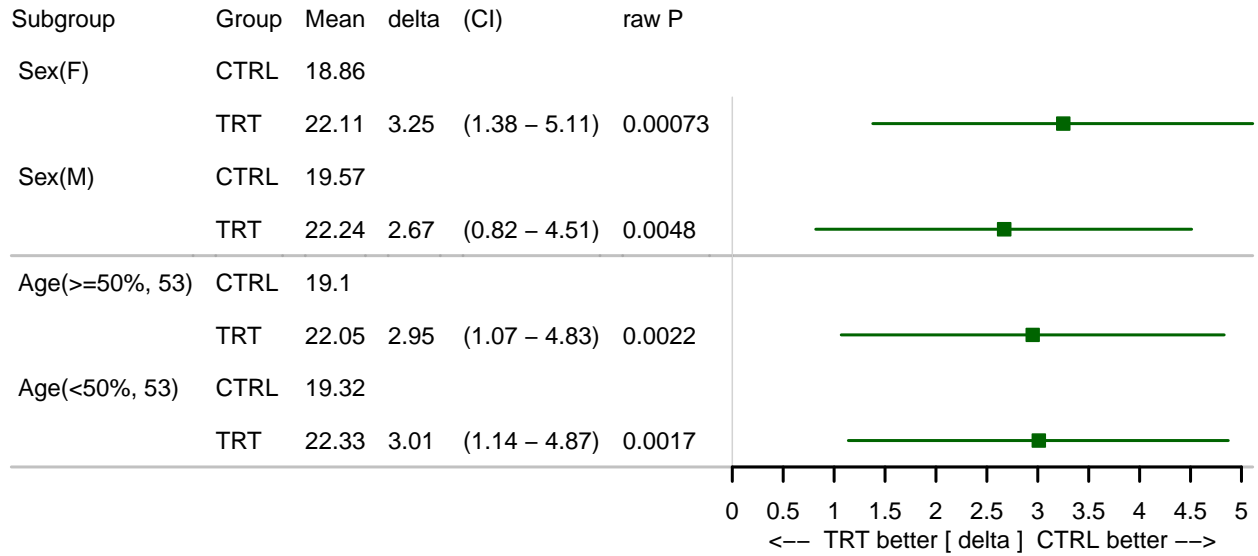
Subgroup	Group	Mean	delta	(CI)	raw P
Sex(F)	CTRL	18.86			
	TRT	22.11	3.25	(1.38 – 5.11)	0.00073
Sex(M)	CTRL	19.57			
	TRT	22.24	2.67	(0.82 – 4.51)	0.0048
Age(>=50%, 53)	CTRL	19.1			
	TRT	22.05	2.95	(1.07 – 4.83)	0.0022
Age(<50%, 53)	CTRL	19.32			
	TRT	22.33	3.01	(1.14 – 4.87)	0.0017

```
0   0.5   1   1.5   2   2.5   3   3.5   4   4.5   5
        <-- TRT better [ delta ] CTRL better -->
```

```
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
```

Across arm
Lab_ontrt

Subgroup	Group	Mean	delta	CI	raw P	Forest plot
						TRT better / CTRL better
Sex(F)	CTRL	18.86				
	TRT	22.11	3.25	1.38 – 5.11	0.00073	
Sex(M)	CTRL	19.57				
	TRT	22.24	2.67	0.82 – 4.51	0.0048	
Age(>=50%, 53)	CTRL	19.1				
	TRT	22.05	2.95	1.07 – 4.83	0.0022	
Age(<50%, 53)	CTRL	19.32				
	TRT	22.33	3.01	1.14 – 4.87	0.0017	

Unadjusted, unstratified analysis

−4 0 2 4
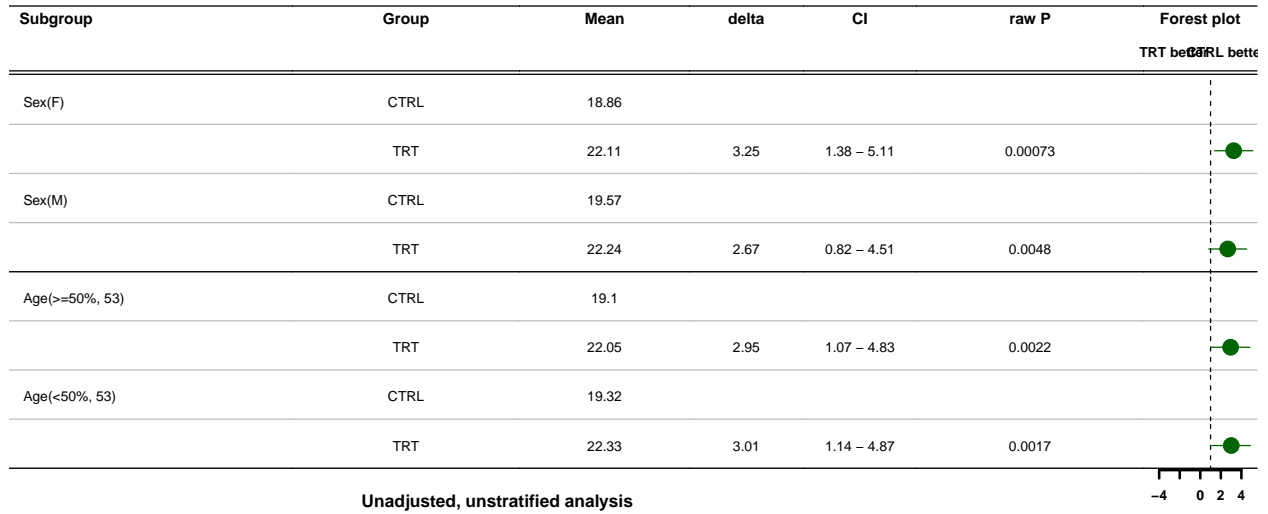
9 PlotSTEPP(): STEPP (Subpopulation Treatment Effect Pattern Plot) from the given point estimates and confidence intervals at desired percentiles.

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
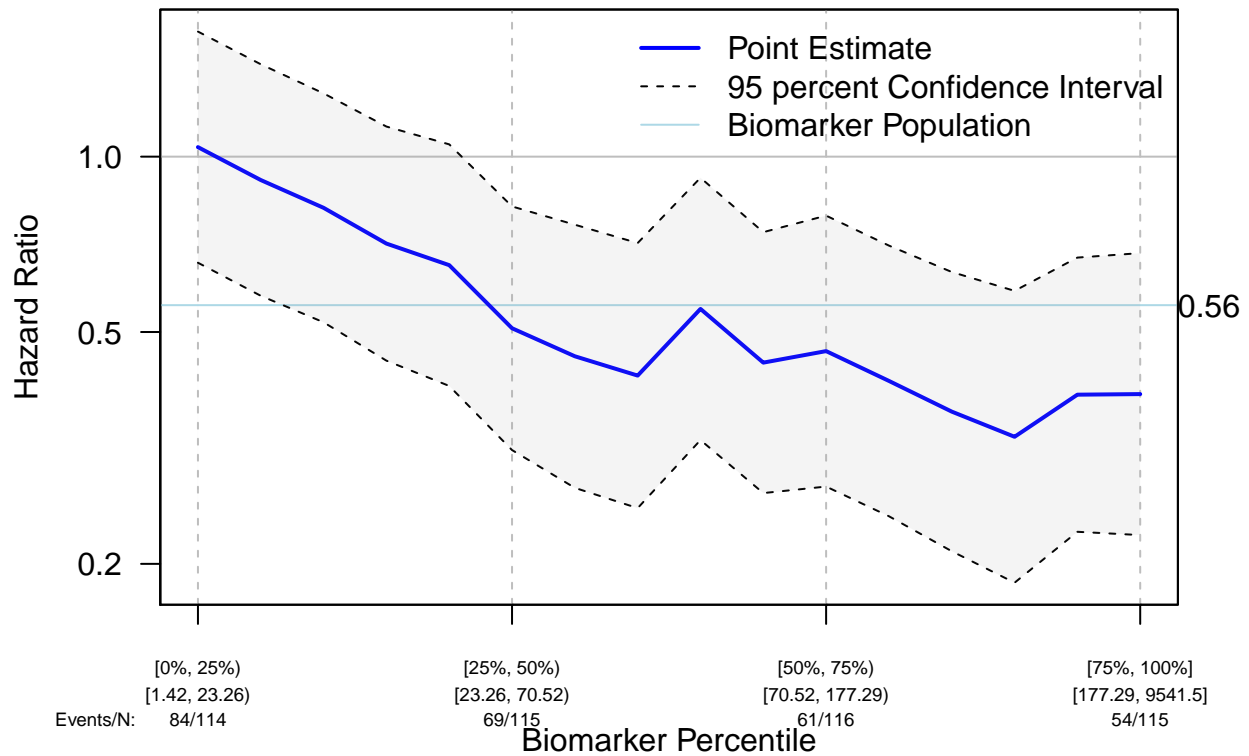

```
##        Window Center Hazard Ratio  CI Lower  CI Upper BM Lower BM Upper
## [1,]         0.125     1.0382905 0.6576013 1.6393629     1.42    23.26
## [2,]         0.175     0.9116623 0.5769829 1.4404727     5.98    32.00
## [3,]         0.225     0.8168277 0.5196594 1.2839325     9.51    42.81
## [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
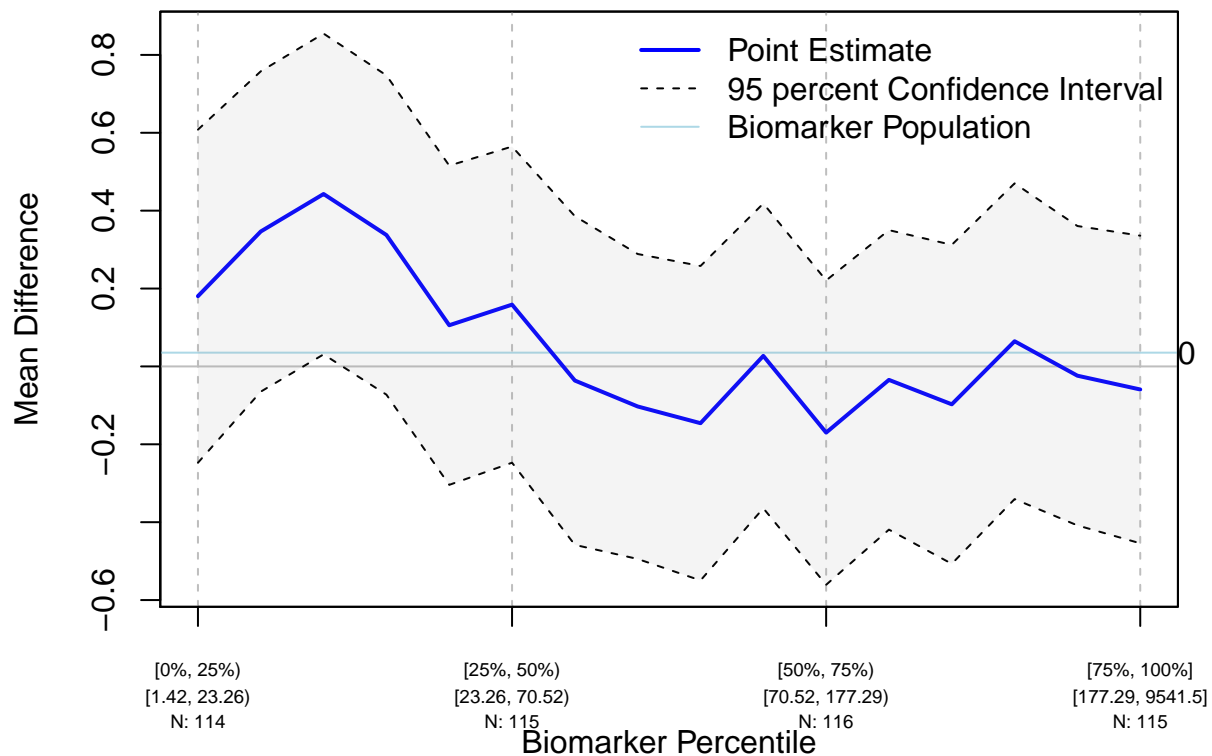
```
##         Window Center Mean Difference    CI Lower  CI Upper BM Lower
## [1,]            0.125      0.18035575 -0.24729997 0.6080115     1.42
## [2,]            0.175      0.34651479 -0.06475305 0.7577826     5.98
## [3,]            0.225      0.44278821  0.03092580 0.8546506     9.51
```

```
##  [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

Proportion Difference (%)

+40
+30
+20
+10
0
−10
−20
−30
−40

Point Estimate
95 percent Confidence Interval
Biomarker Population

3%

[0%, 25%)   [25%, 50%)   [50%, 75%)   [75%, 100%]
[1.42, 23.26)   [23.26, 70.52)   [70.52, 177.29) [177.29, 9541.5]
N: 114   N: 115   N: 116   N: 115

Biomarker Percentile
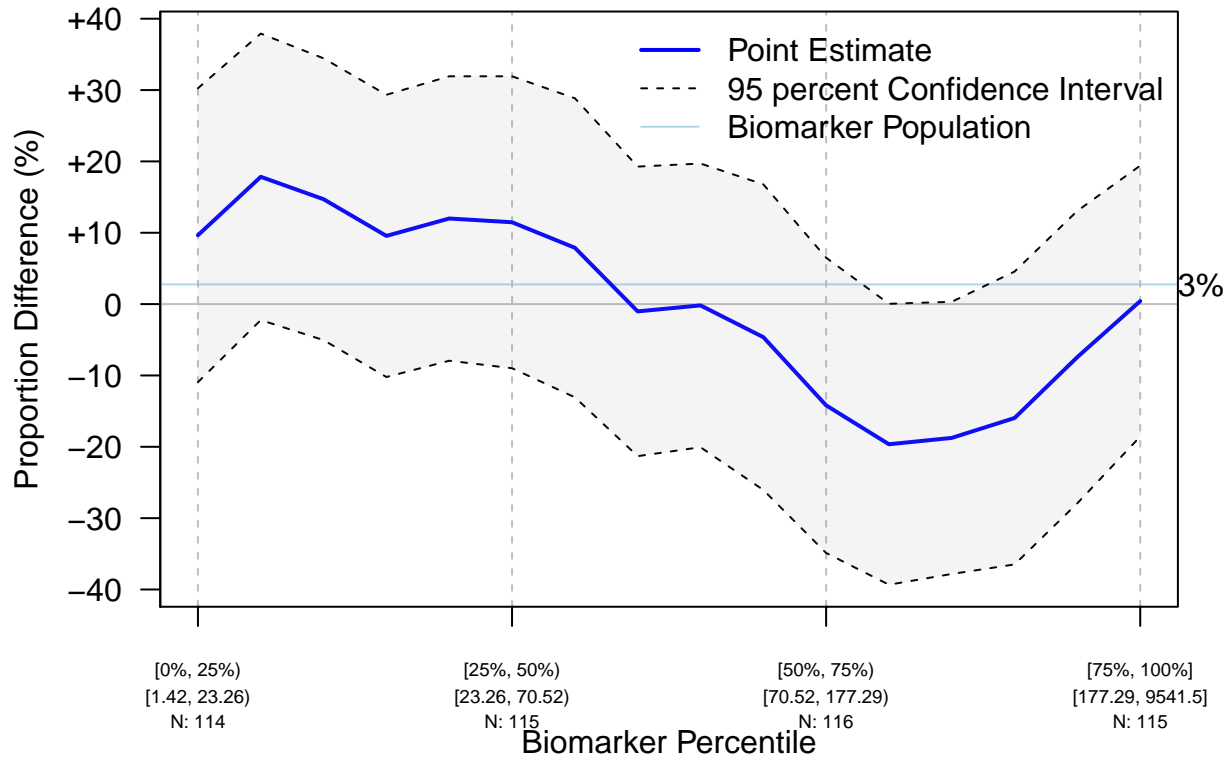
```
##      Window Center Proportion Difference   CI Lower    CI Upper
## [1,]        0.125            0.096558637 -0.10936788 0.3024851571
## [2,]        0.175            0.178408350 -0.02235039 0.3791670900
## [3,]        0.225            0.147000659 -0.05041839 0.3444197101
## [4,]        0.275            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=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   StatSummary()

11.1   Contunuous outcome

11.1.1   Create summary statistics

```
StatSummary(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

```
StatSummary(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

```
StatSummary(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

```
StatSummary(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

```
StatSummary(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
##  38.0000000   182.0000000   14.8829569    59.0000000   368.0000000            NA
## Effect.Size        Lower         Upper             P
##   0.6667451    0.4432032     1.0030365     0.0517253
```

11.3.2 Add a covariate variable

```
StatSummary(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   182.00000000   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

```
StatSummary(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 N=182	TRT 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  9.317749   t2   2   1
## 2 10.530510   t2   1   2
## 3 10.340731   t2   1   2
## 4  8.868233   t2   3   2
## 5  9.533215   t2   1   1
## 6  9.614363   t2   3   2
```

```
str(example)
```

```
## 'data.frame':    50 obs. of  4 variables:
##  $ y   : num  9.32 10.53 10.34 8.87 9.53 ...
##  $ time: Factor w/ 4 levels "t1","t2","t3",..: 2 2 2 2 2 2 2 2 2 2 ...
##  $ grp : int  2 1 1 3 1 3 2 3 2 1 ...
##  $ sex : int  1 2 2 2 1 2 2 2 1 2 ...
```

13.2 Specify data as named list

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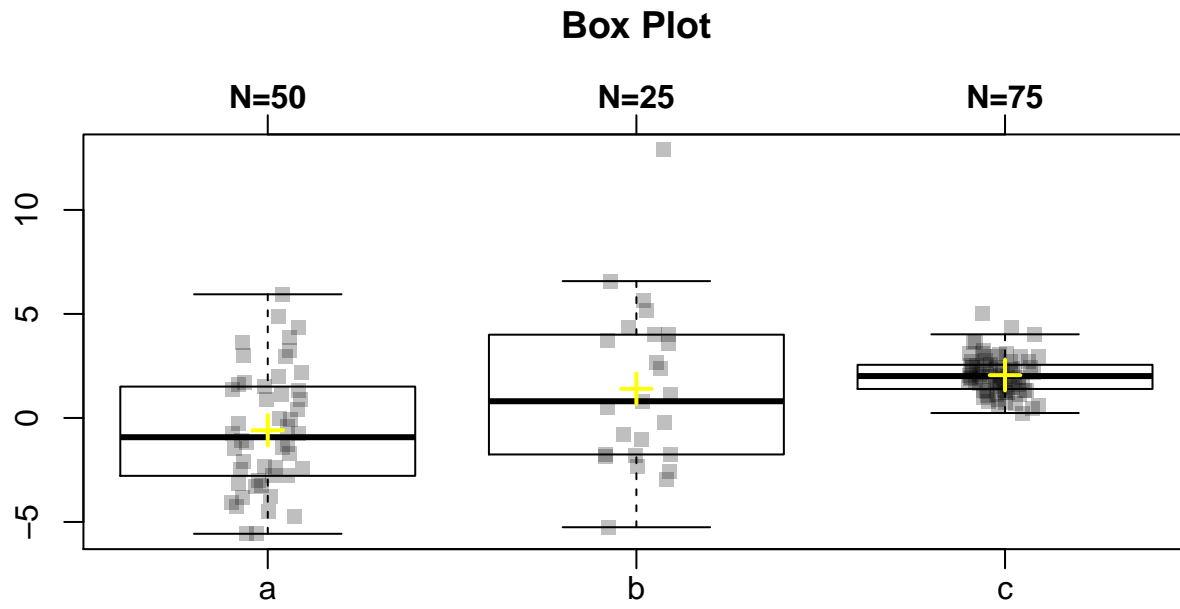
Box Plot

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))
```
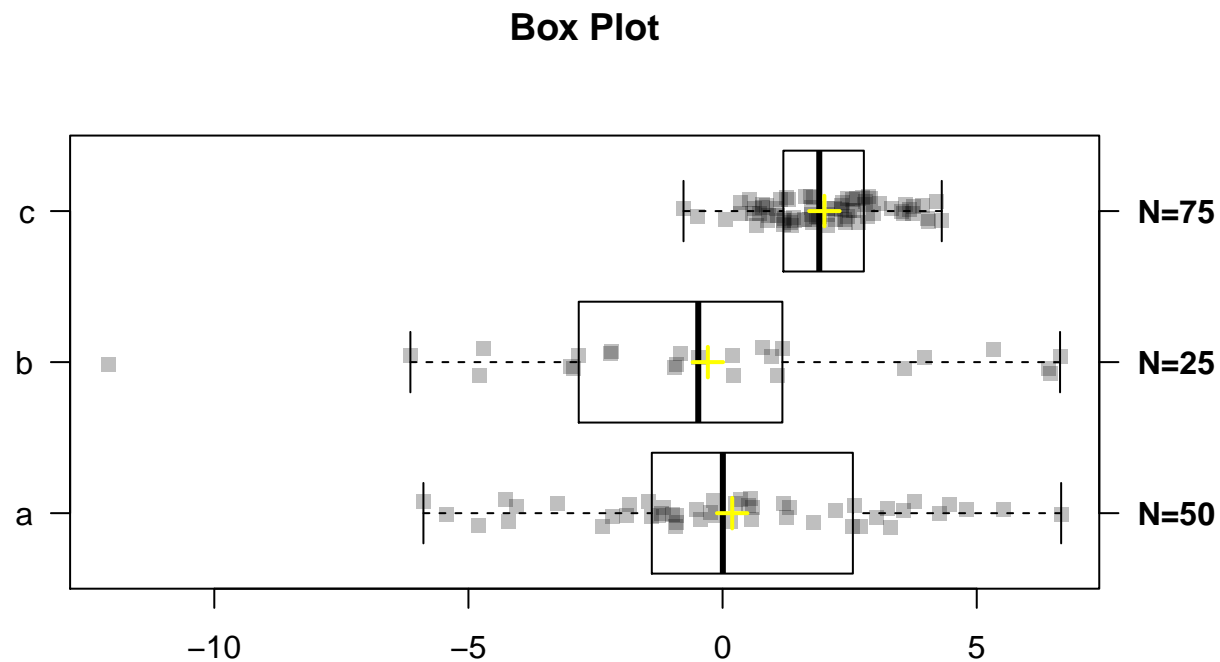

Box Plot

13.4 Specify data as numeric matrix

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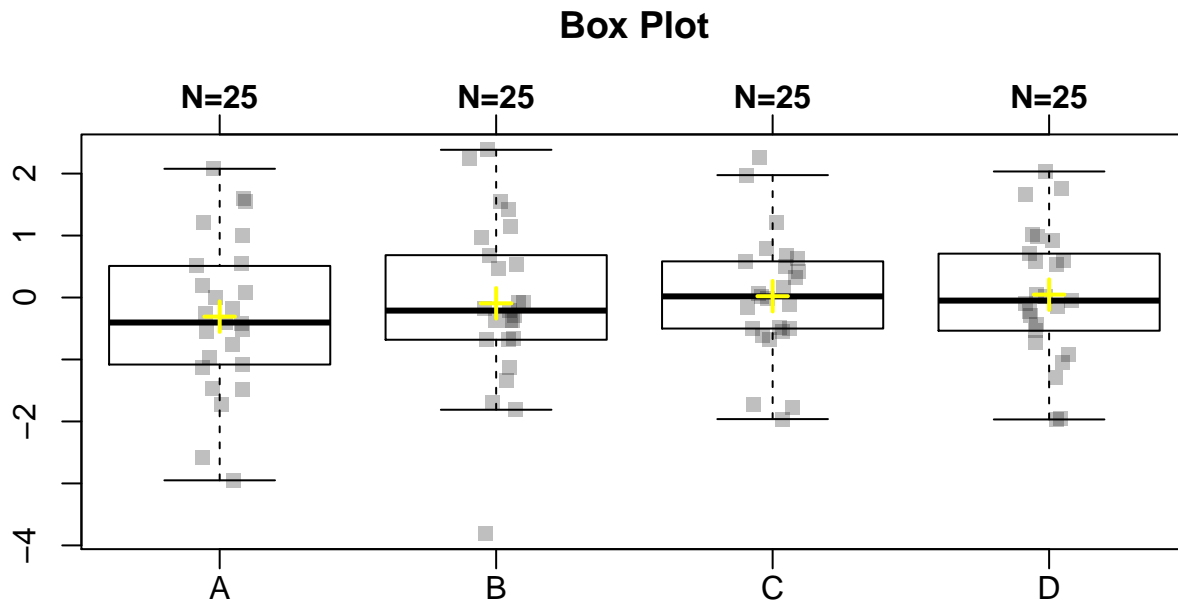
Box Plot

13.5 Specify data as numeric (unnamed) vectors

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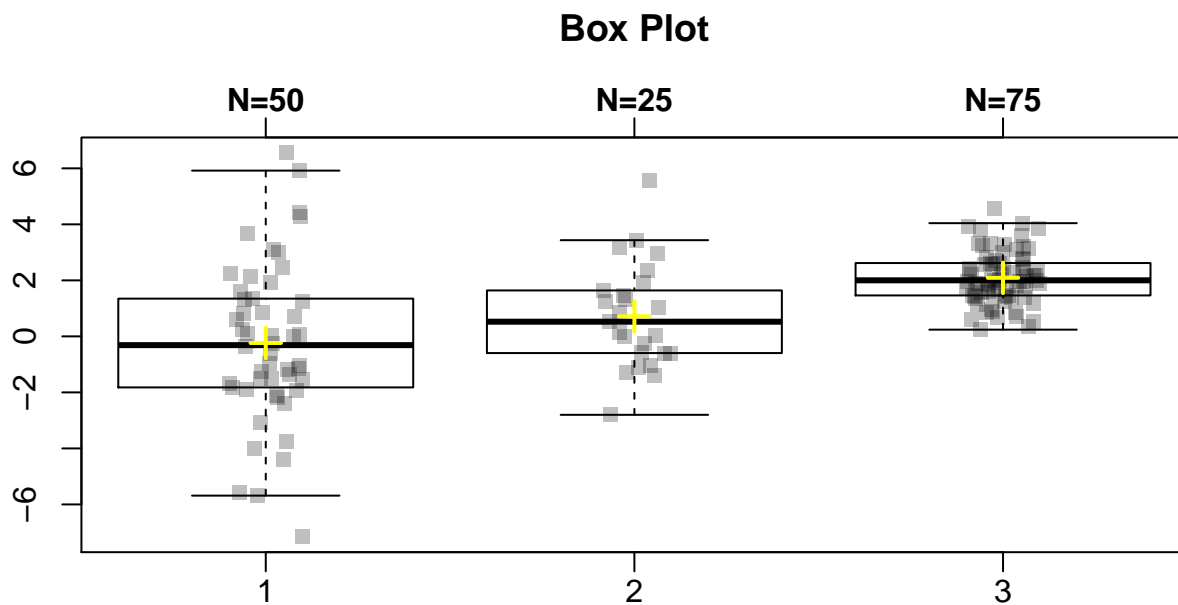
Box Plot

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

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

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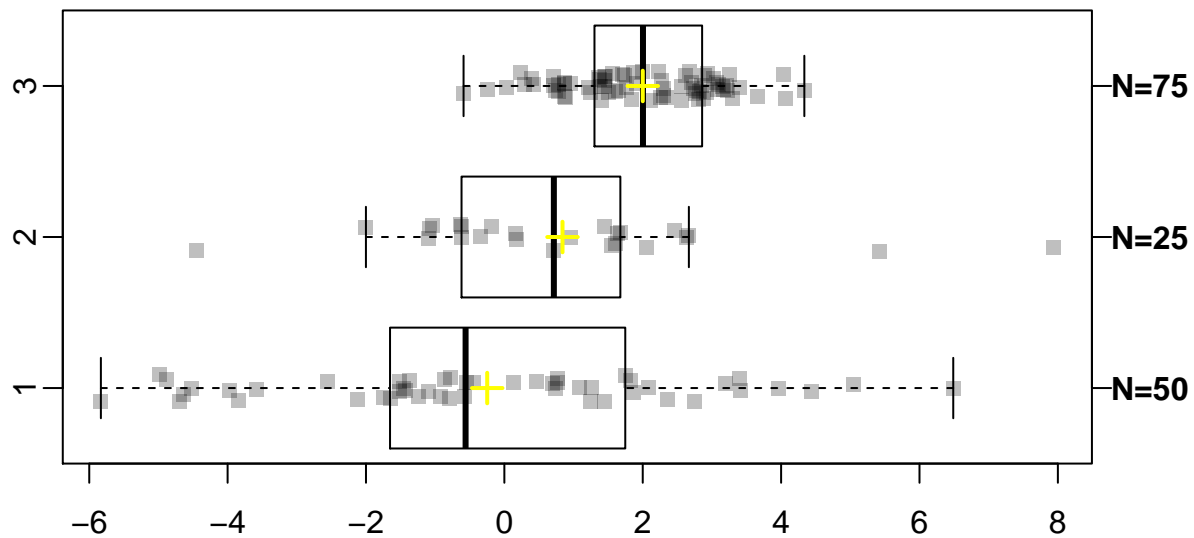
13.7 Plot values 'y' according to time 'time' (factor levels are automatically ordered as e.g. function sort does)

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

Box Plot
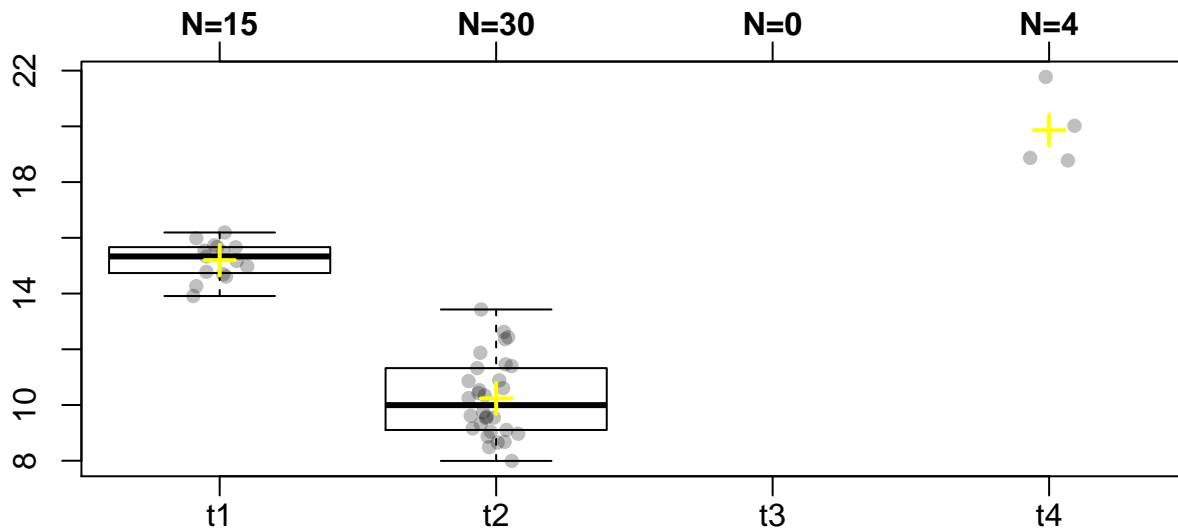
13.8 Now as box-percentile plot

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

Box–Percentile Plot
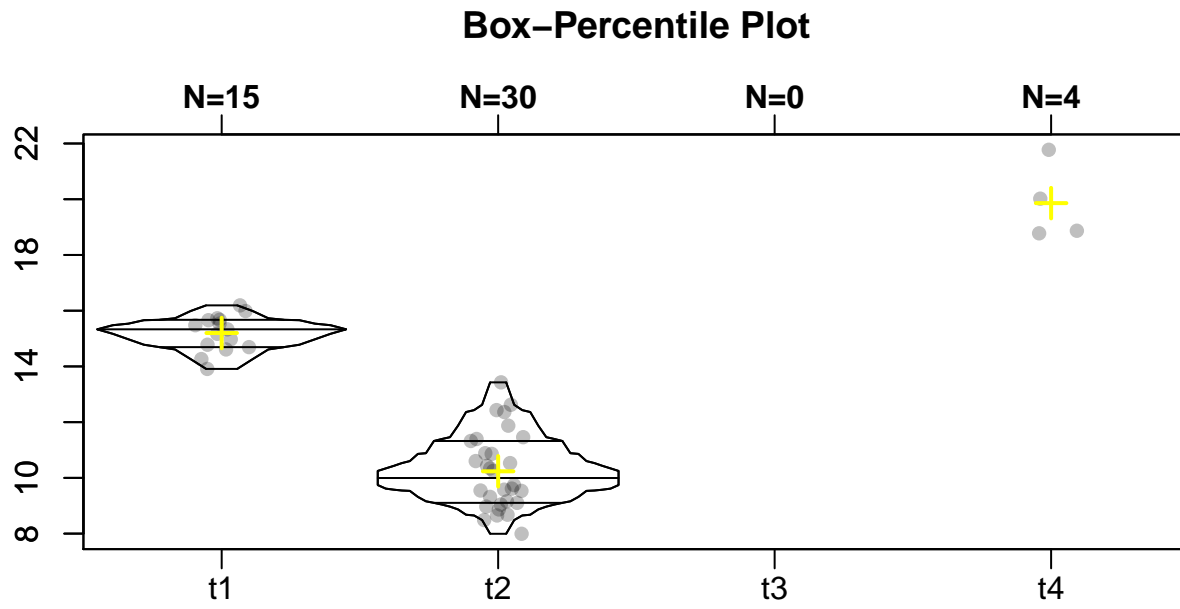
13.9 With custom main title

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

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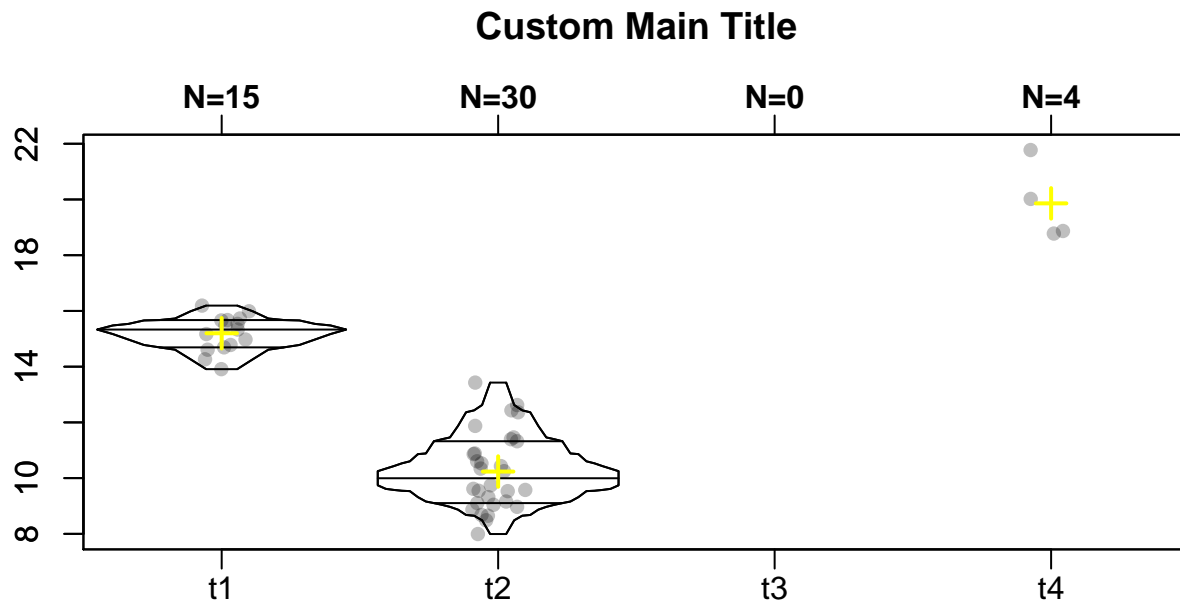
13.10 The same plot with trend line (connects either means or medians) and Y-axis label

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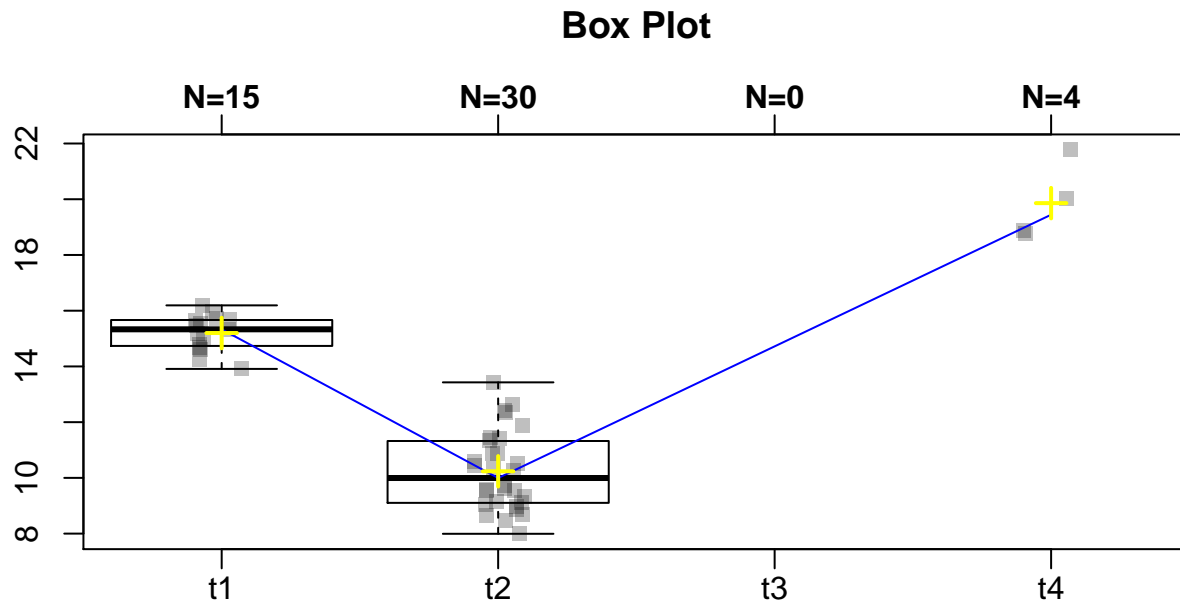
Box Plot

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] )
```
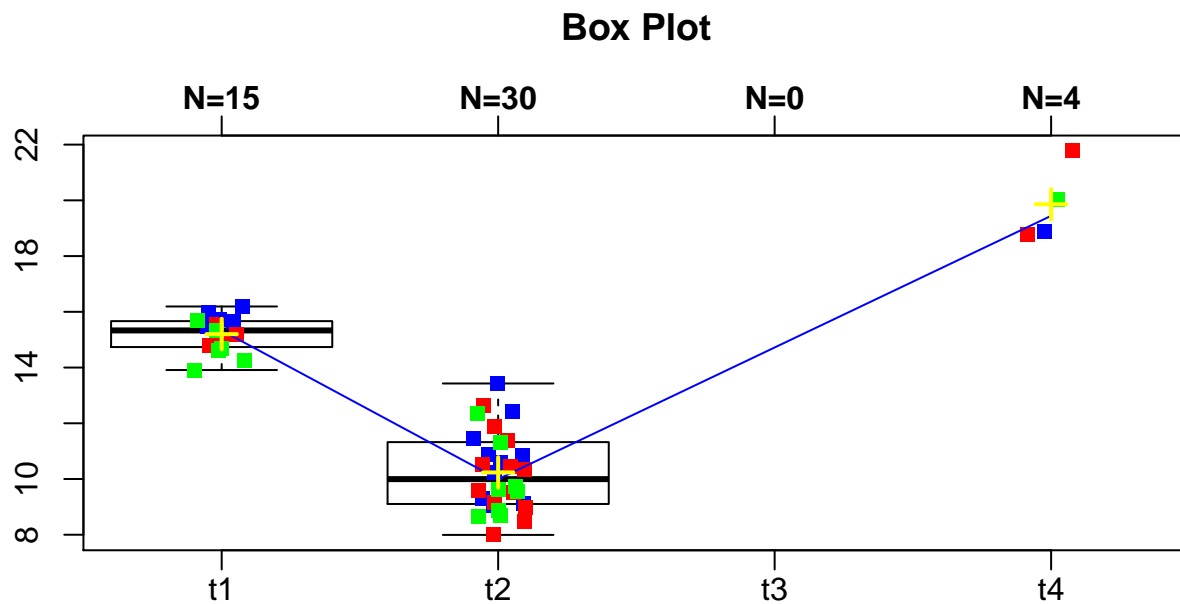
Box Plot

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] )

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)
```
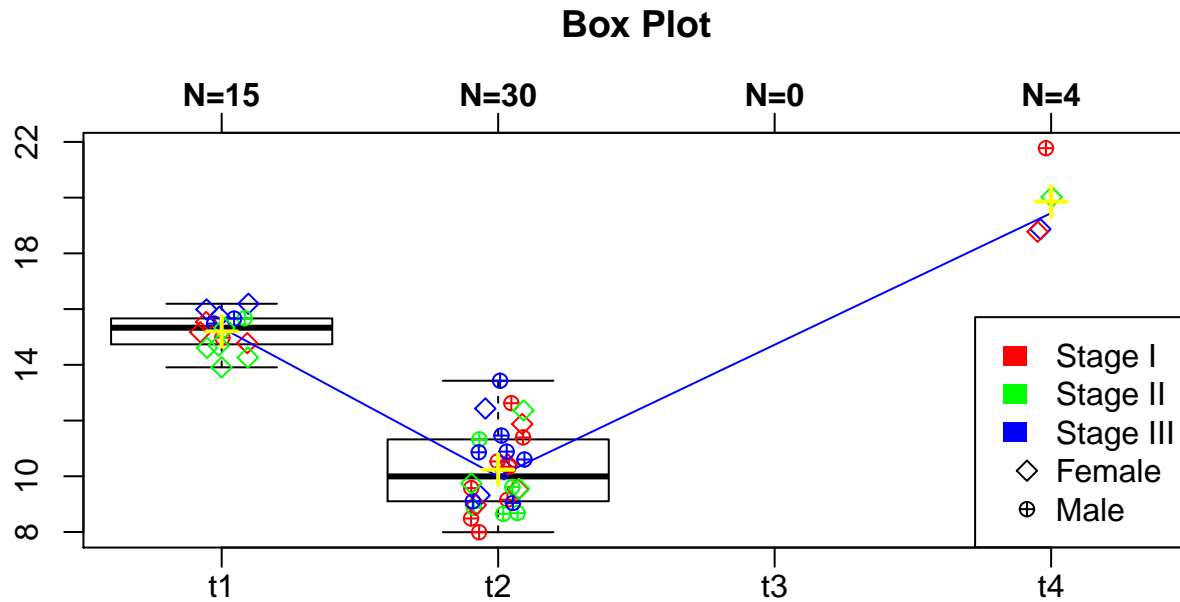

13.13 Generate new dataset with different stucture

```
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")
```
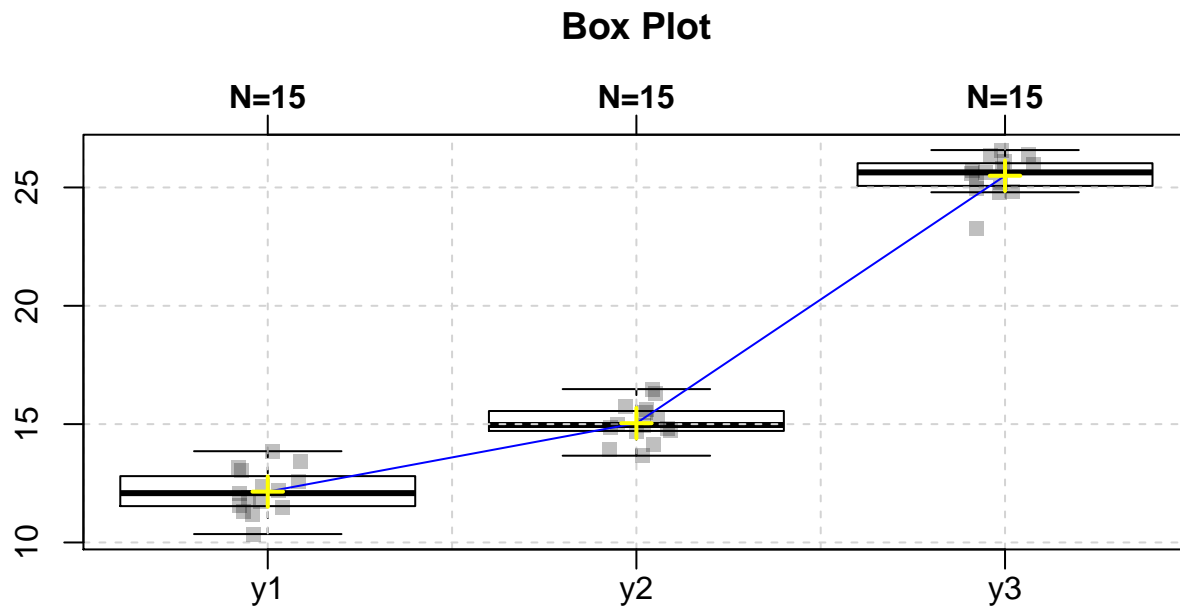
13.15 Now as box-percentile plot

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

Box–Percentile Plot
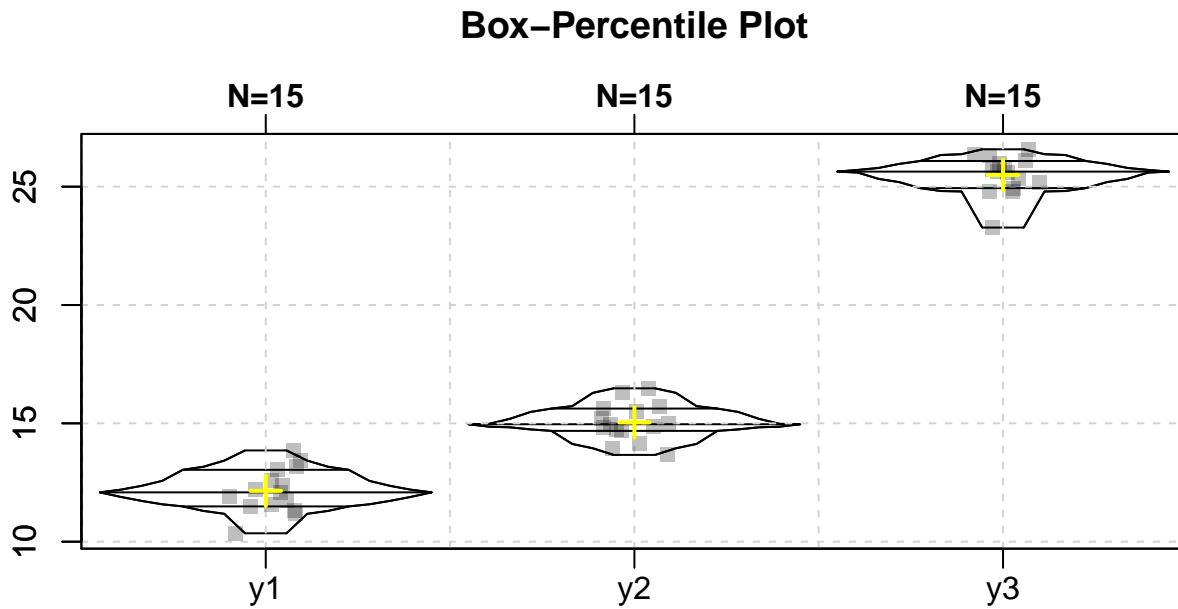
13.16 Use yet another way to specify the data

```
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))
```

Box–Percentile Plot
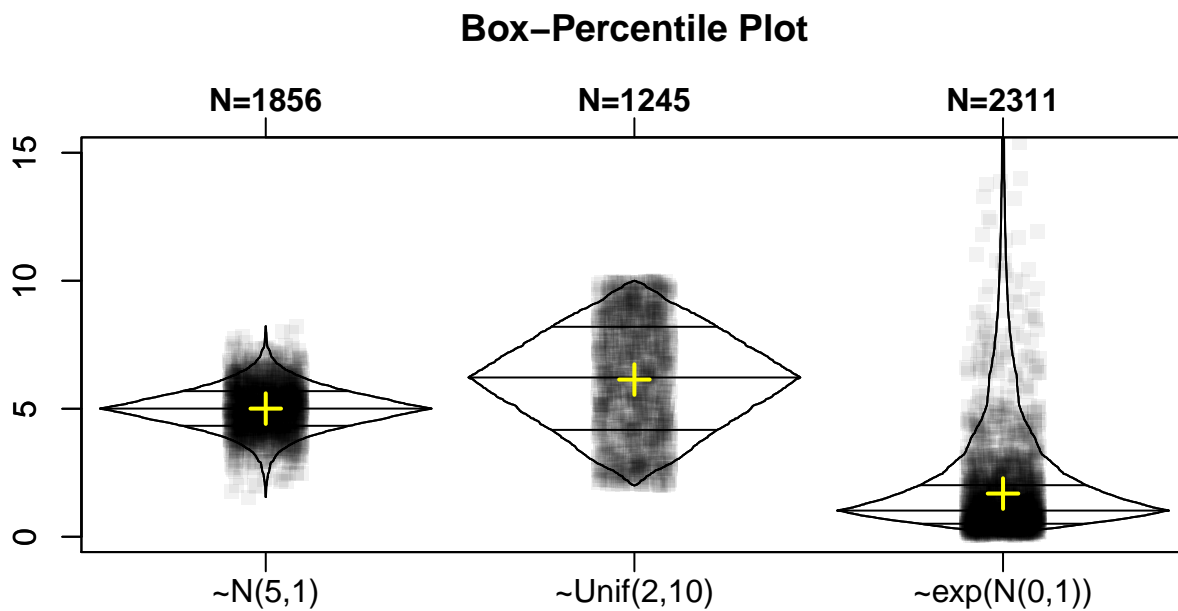
13.17 Specifying data as numeric matrix and using a trend-line connecting the means

```
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"))
```
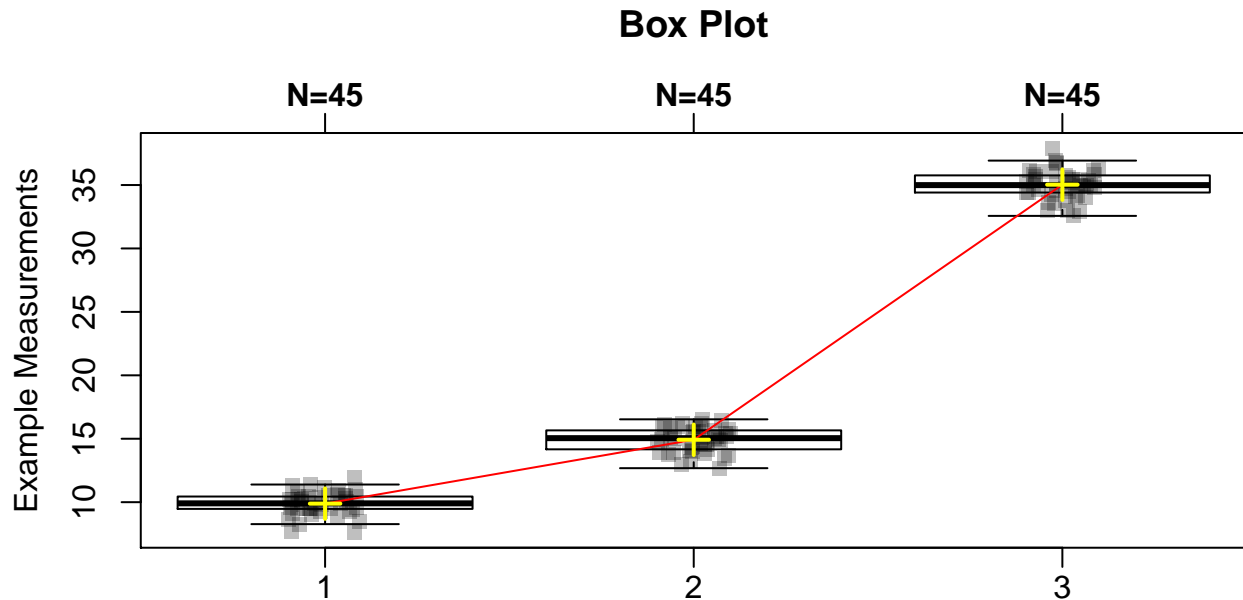

13.18 Multiple grouping factors can be specified via the formula interface which is exemplified using the mtcars dataset, of interest is miles per gallon (mgp) depending on number of gears and on the number of cylinders

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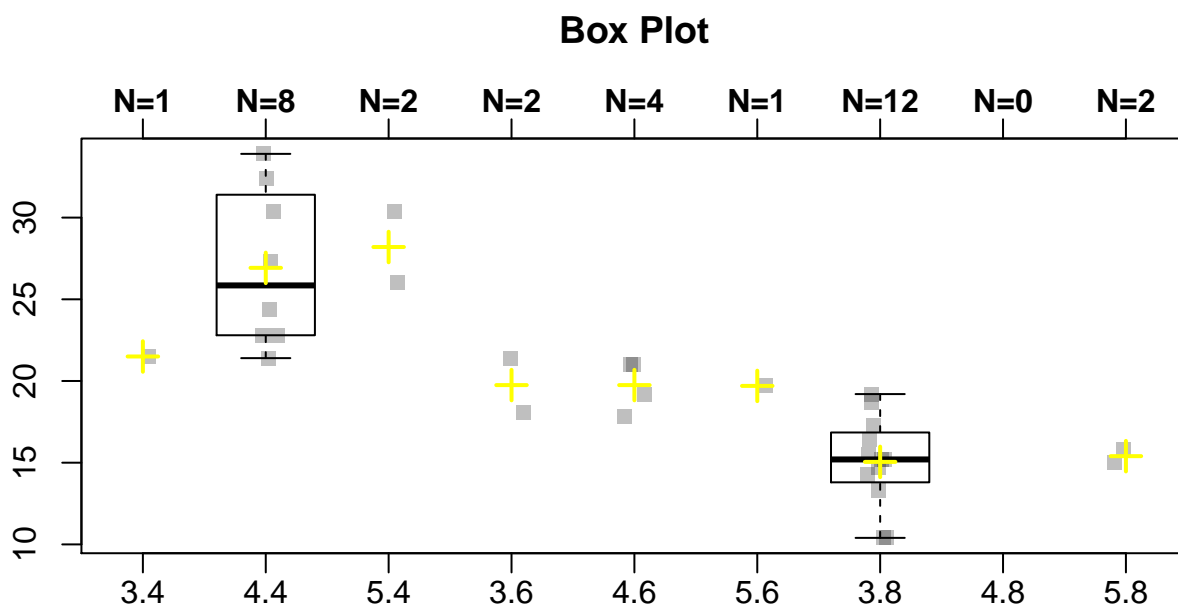
13.19 Now 'cyl' is explicitly nested within 'gear' which changes the ordering of combined grouping factors (which is identical to using formula 'mpg~cyl:gear').

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

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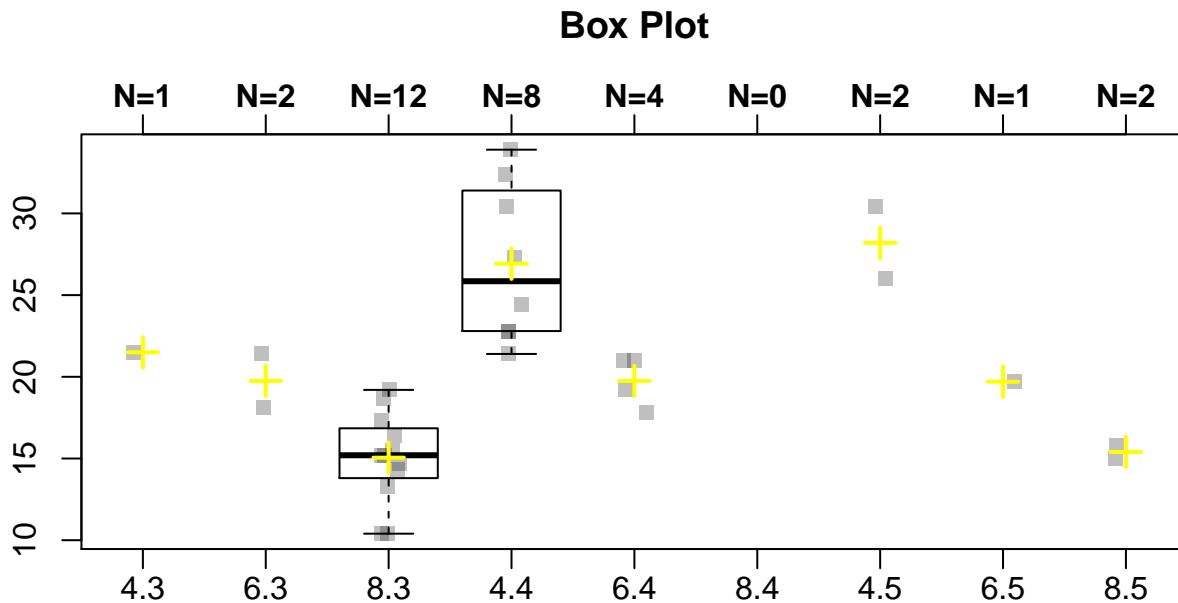
13.20 More meaningful group-labels are best specified using custom factor-level names (increase width of the plot window)

```
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)
```
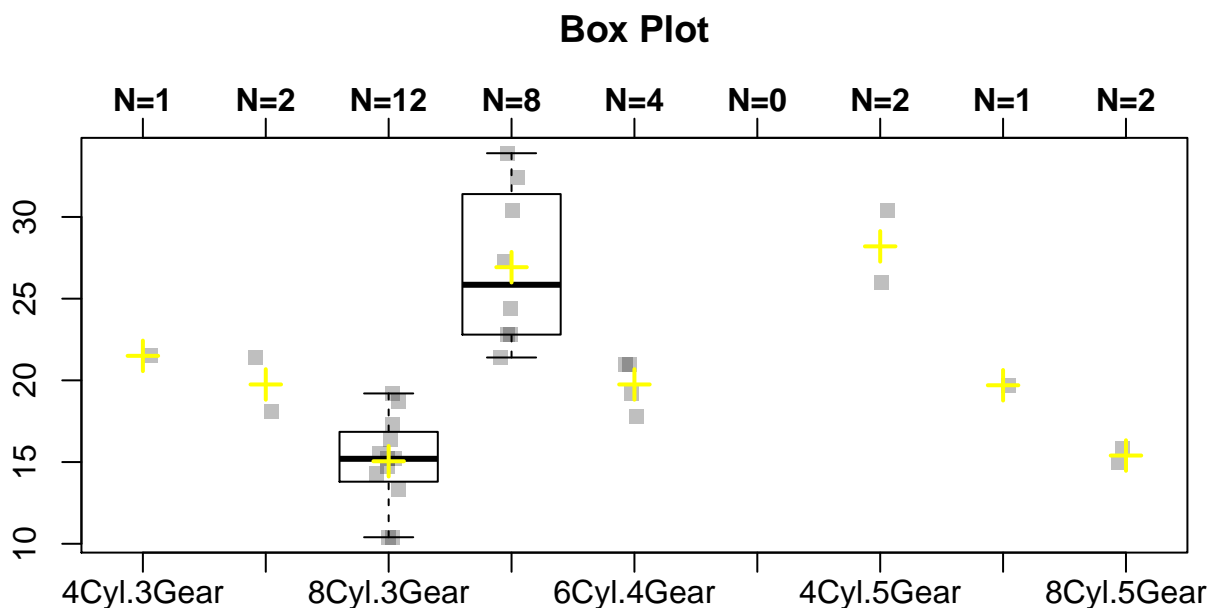
Box Plot

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))
```
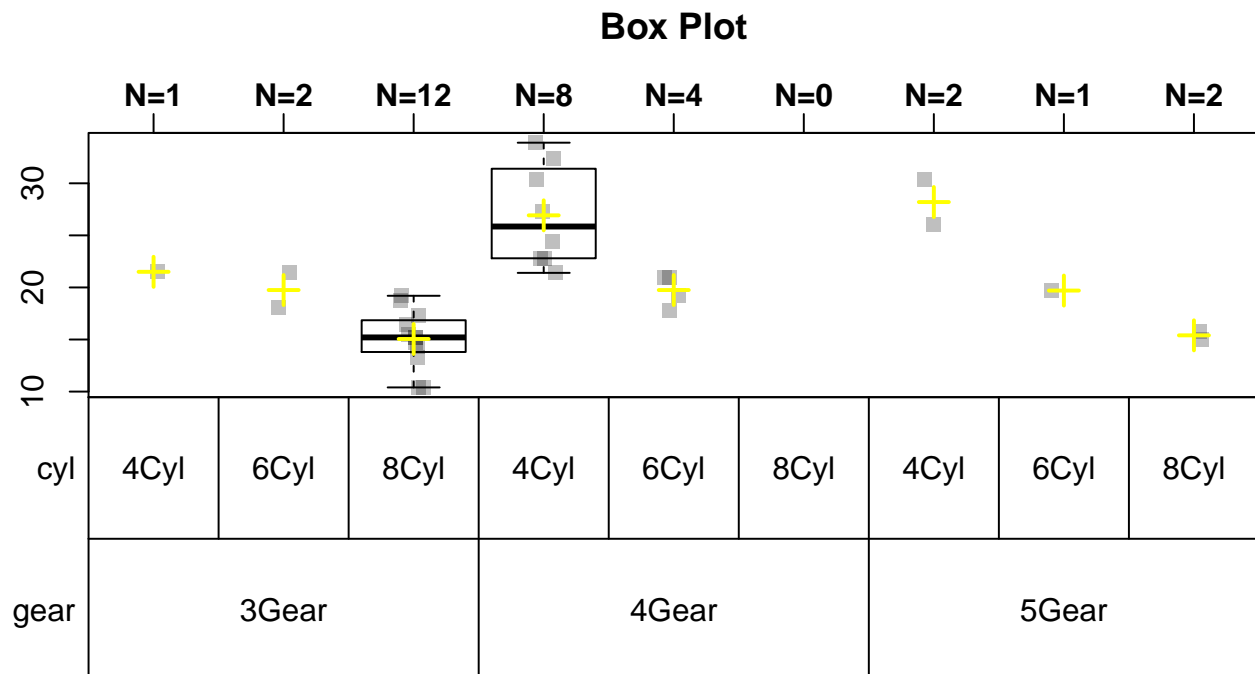

13.22 With the original factor levels and as horizontal plot

```
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"))
```
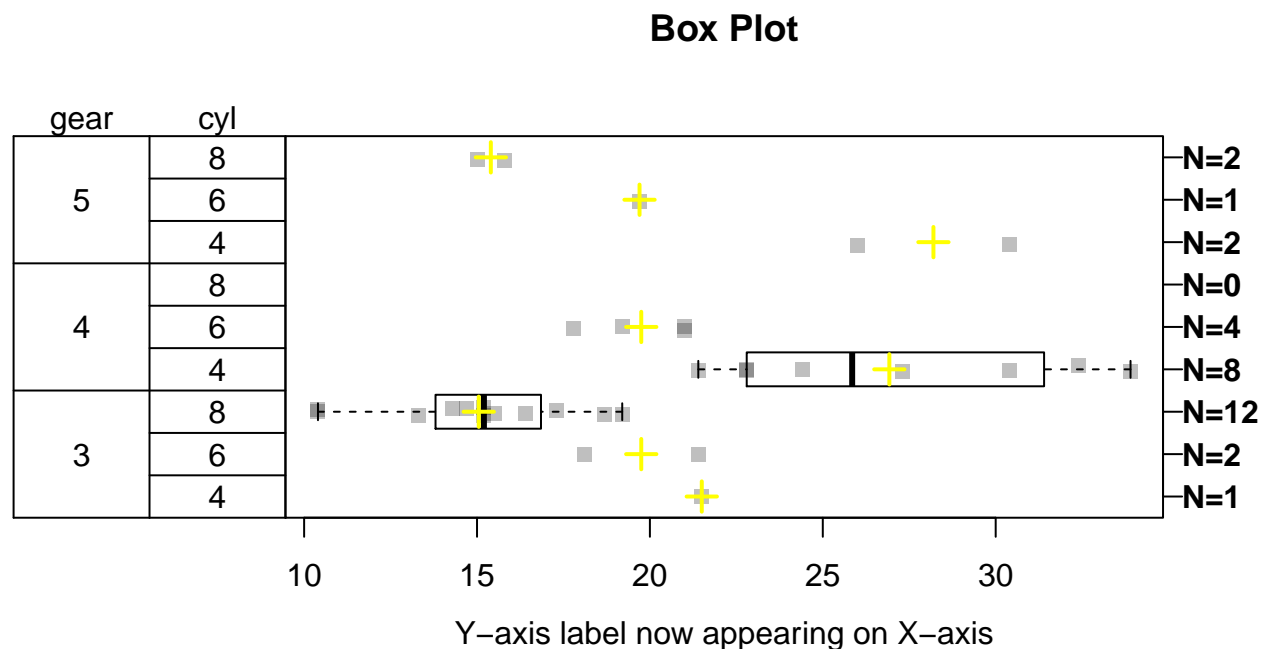
13.23 Using smaller bottom margin will result in smaller table height

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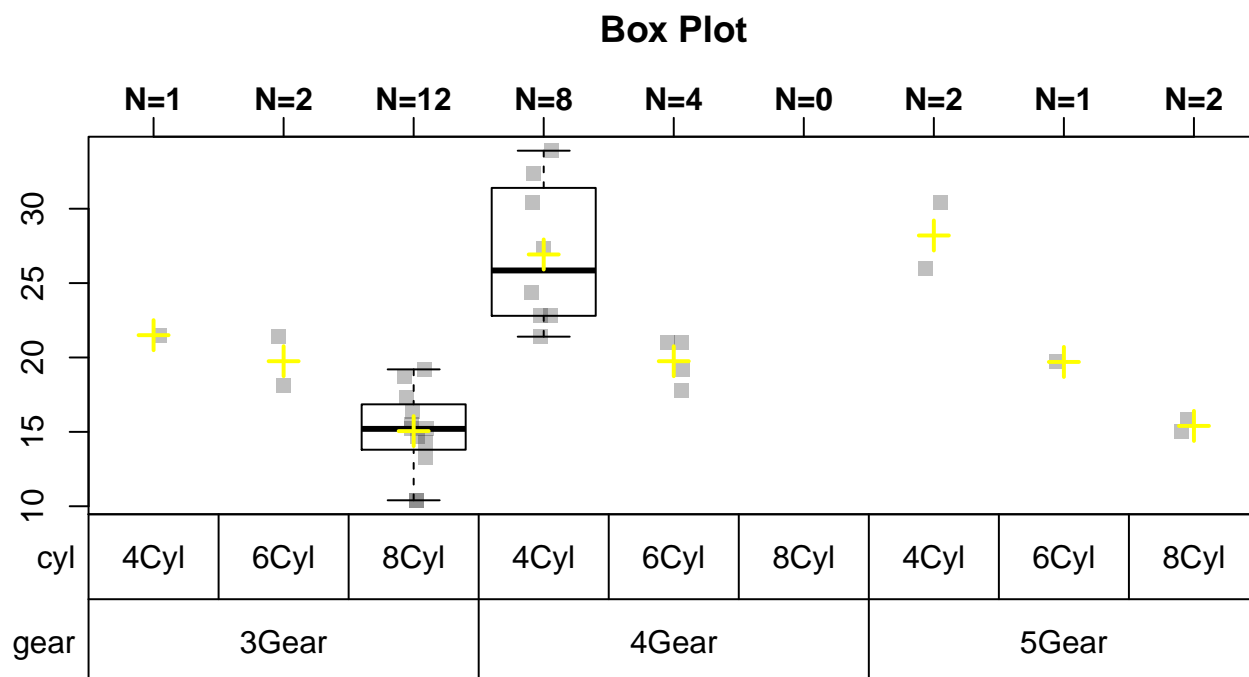

13.24 One can use different font-settings for rownames and cells of the table

```
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))
```
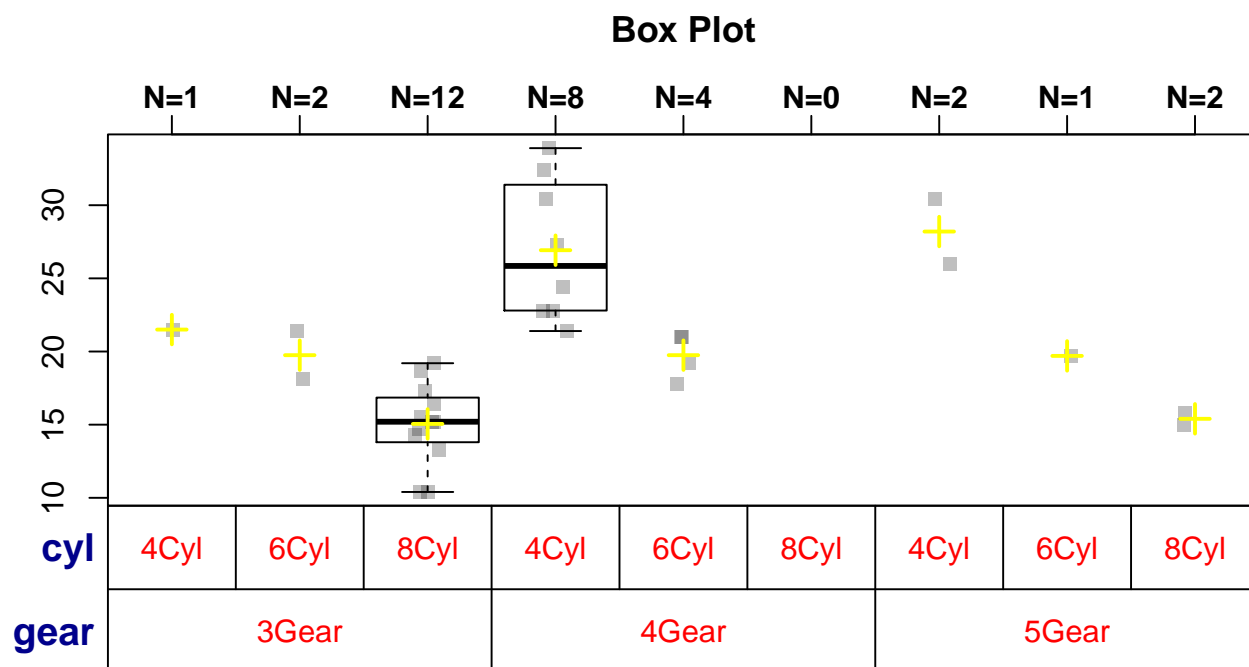
13.25   Use more crossed factors

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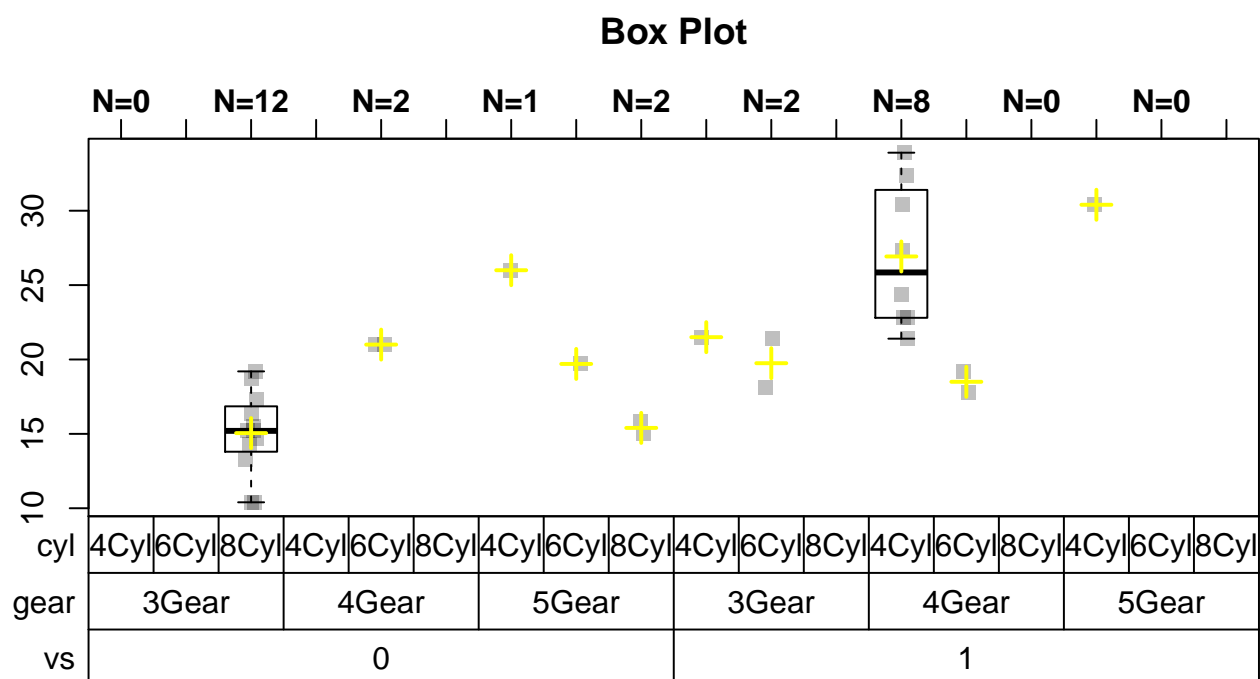
Box Plot

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=".")))
```
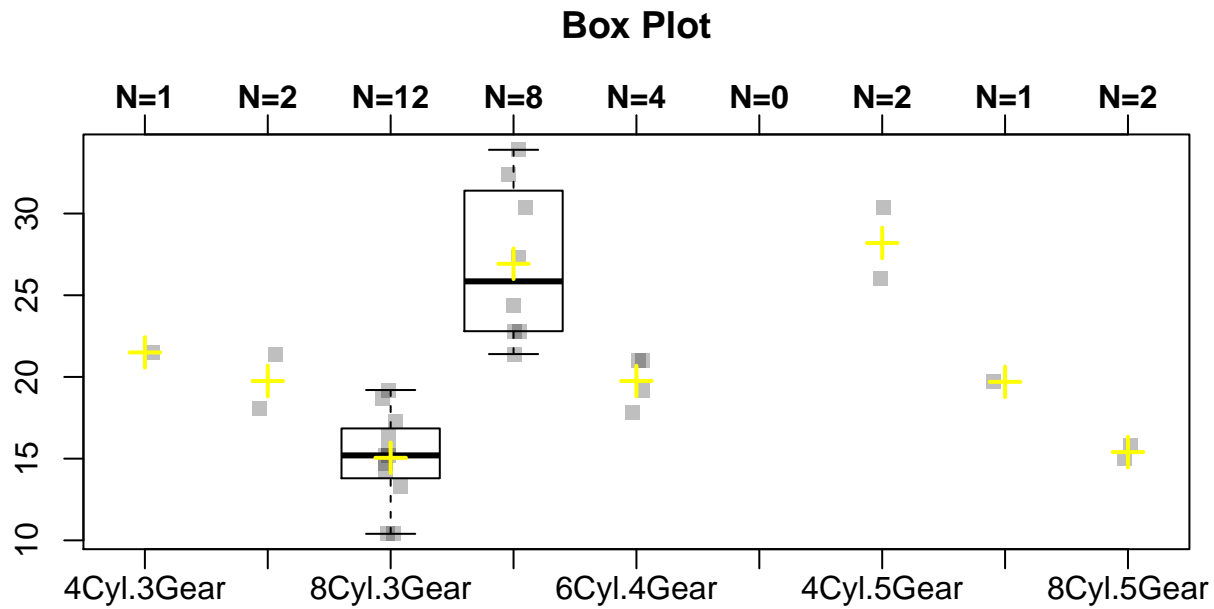
Box Plot

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",
     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), re
                 at=1:9, las=2, adj=1, line=0.75, col=c(rep("blue", 3), rep("red", 3), rep("green"
     mean.col=c(rep("cyan", 3), rep("orange", 3), rep("magenta", 3)), Box=FALSE, trend="mean",mar=
```


Miles per Gallon by Number of Gear
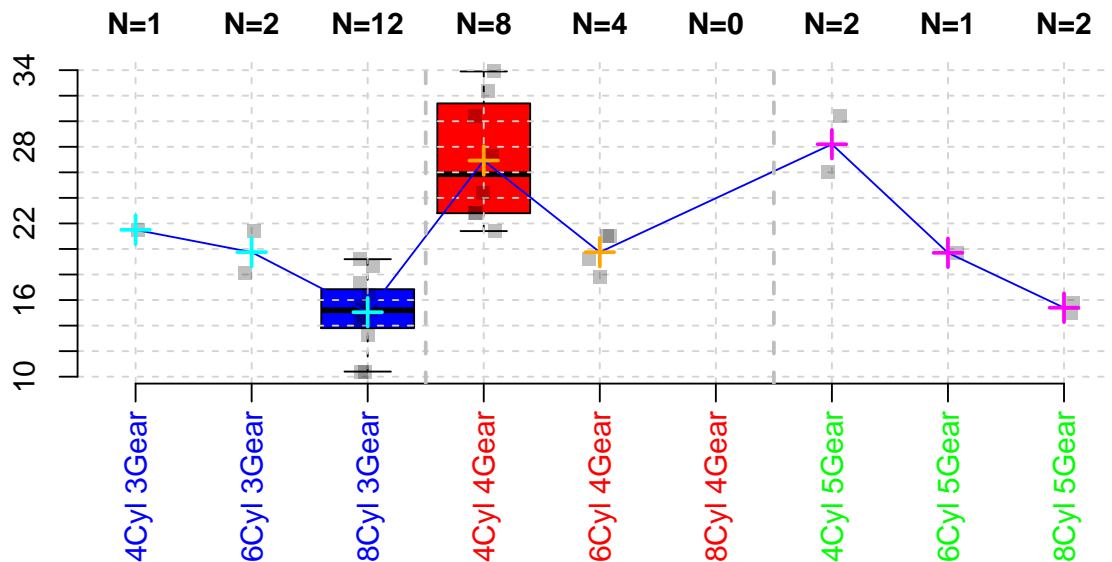
13.28 Horizontal fancy plot

```
BoxPlot(mtcars, mpg~cyl %in% gear, Title=list(main="Miles per Gallon by Number of Gears", col.main="#84c
        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(1
        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")
```
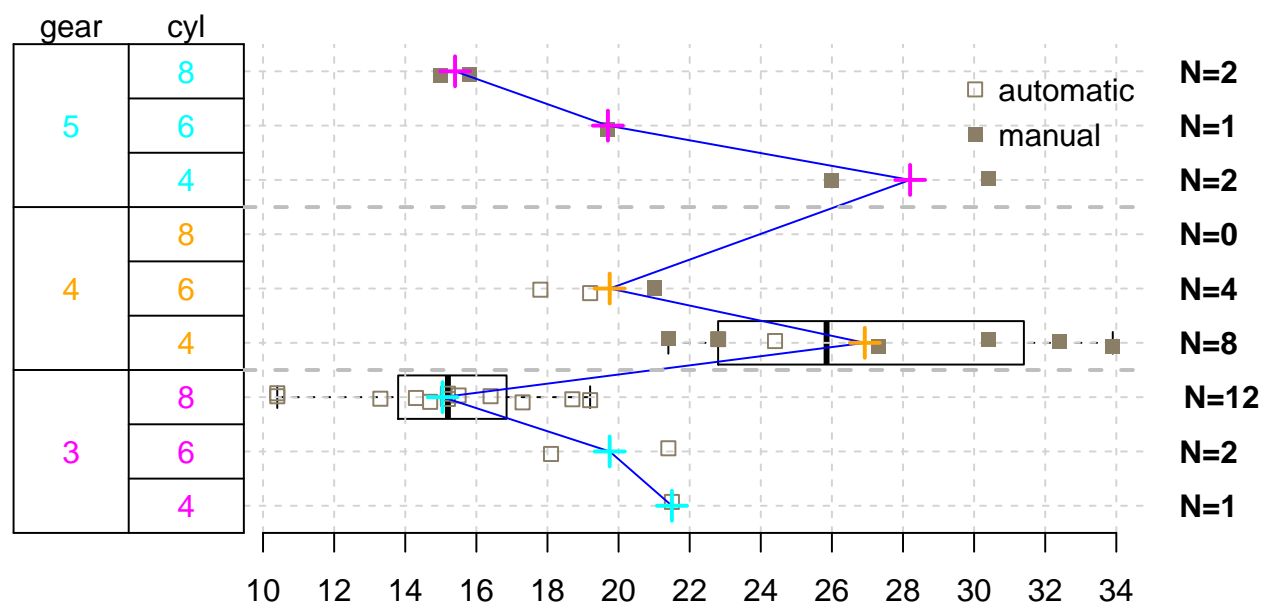

14 Longitudinal analysis

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')
```
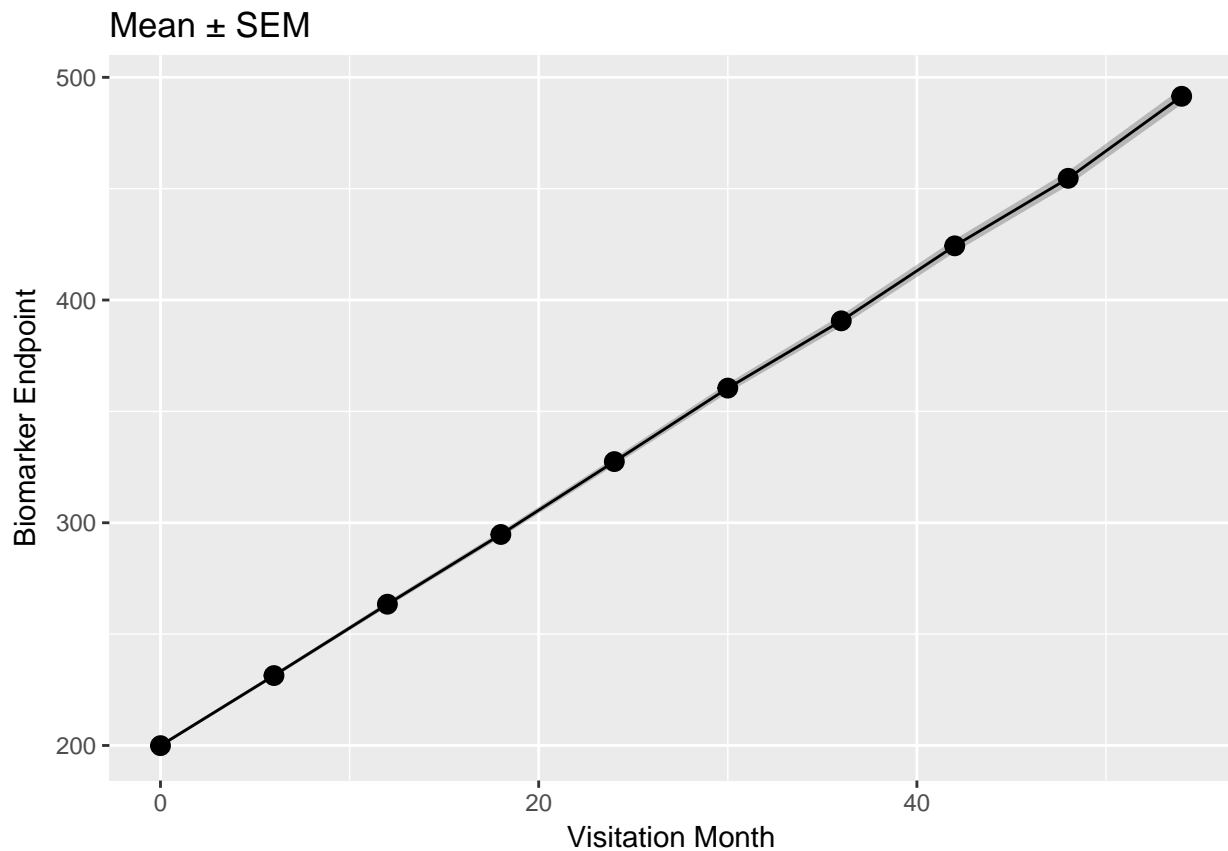
14.1.2 Tukey Hinges and Whiskers

However, we may be more interested in the population distrubtion 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.
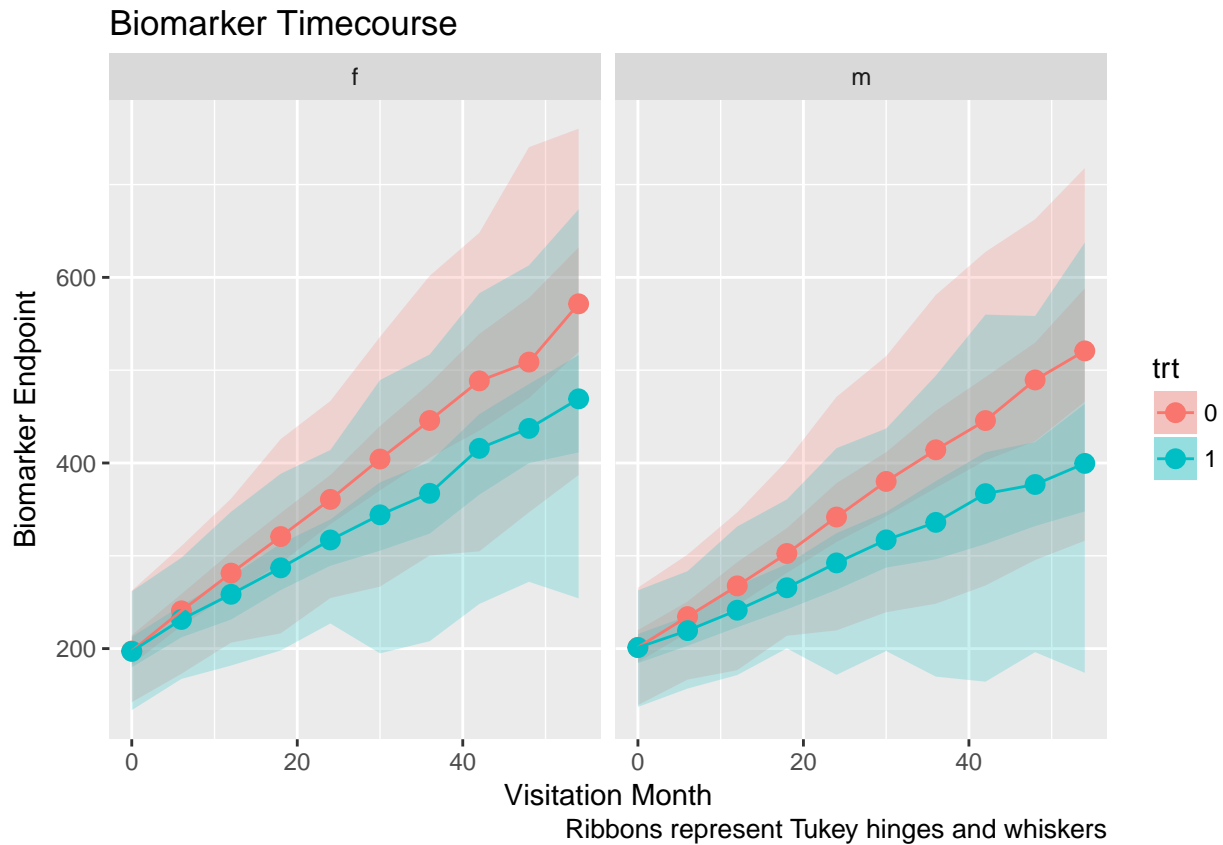
```
PlotLong(longbmkr, aes(x=vm, y=ep), fun.data = 'tukey',
        xlab = 'Visitation Month',
        ylab = 'Biomarker Endpoint',
        labs.title = 'Tukey Whiskers and Hinges')
```

Tukey Whiskers and Hinges
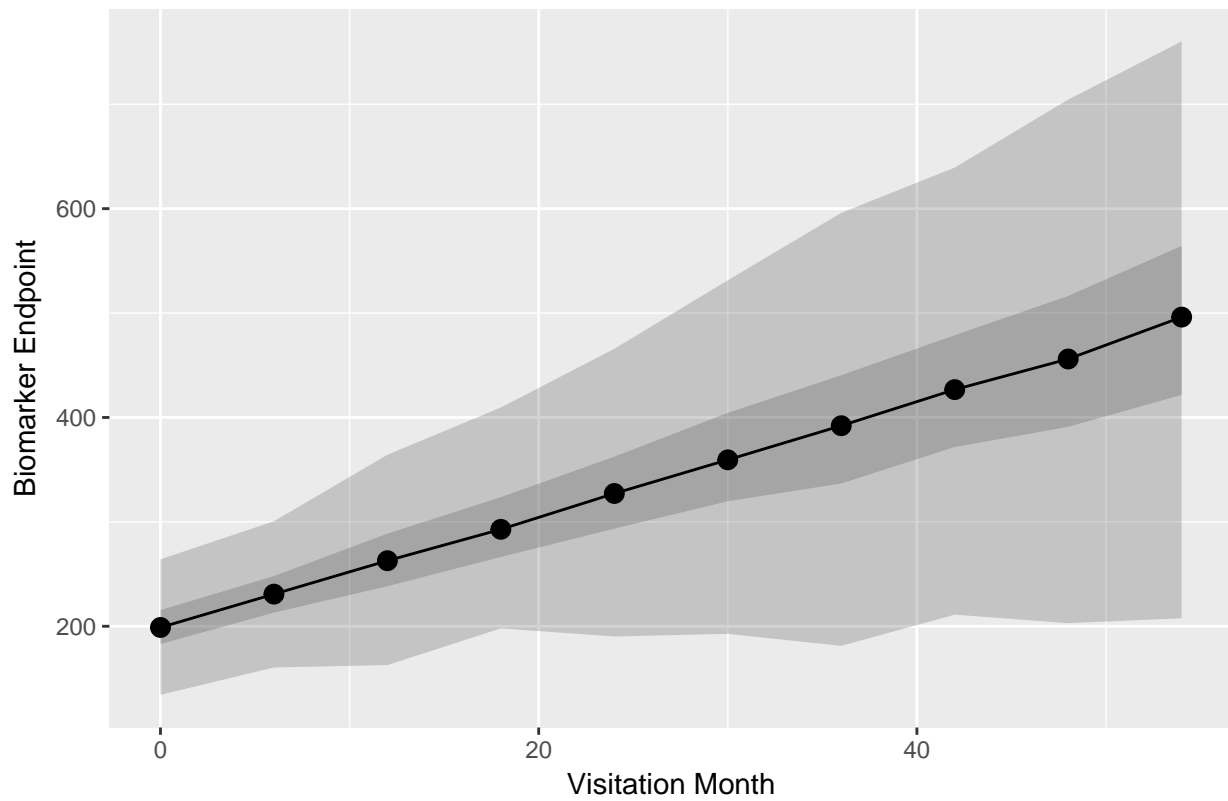
14.2   Plotting Subpopulations

```
PlotLong(longbmkr, 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')
```

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14.3 Including sample counts

14.3.1 Sample counts as table above plot

```r
library(dplyr)
```

```
## Warning: package 'dplyr' was built under R version 3.3.2
```

```
##
## Attaching package: 'dplyr'
```

```
## The following objects are masked from 'package:stats':
##
##     filter, lag
```

```
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
```

```r
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')
```

```
## Warning: package 'bindrcpp' was built under R version 3.3.2
```

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Ribbons represent Tukey hinges and whiskers
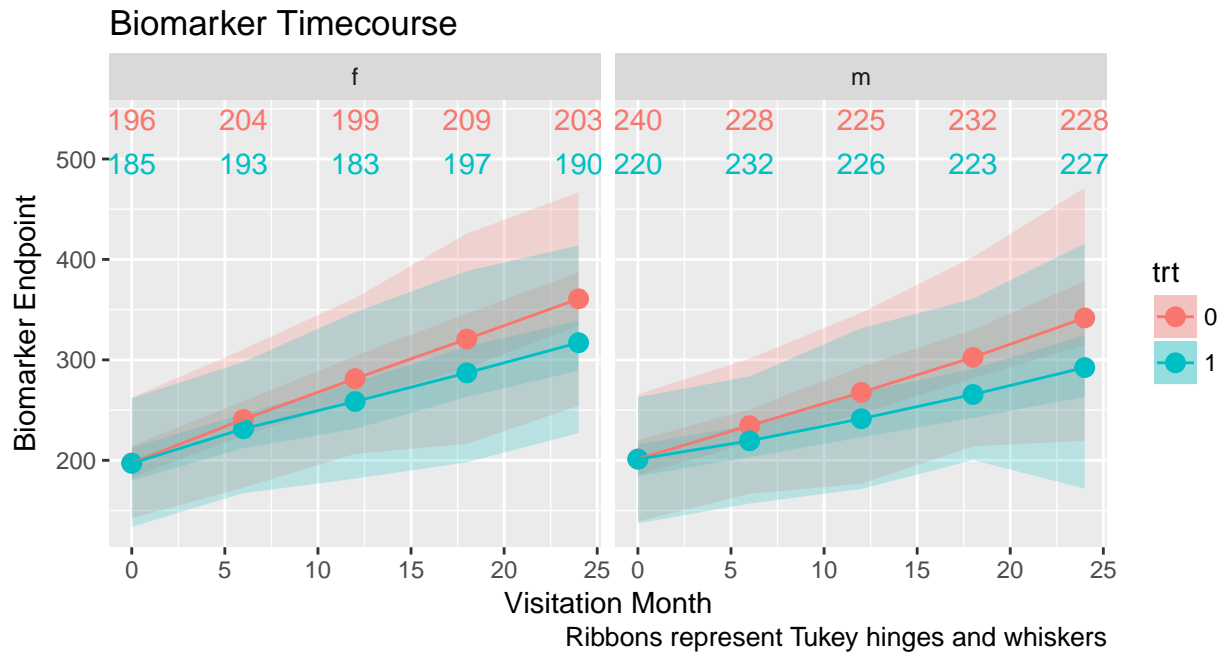
14.4   Plotting Deviations as Errorbars

```
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',
        plot.style = 'errorbars',
        xlab = 'Visitation Month',
        ylab = 'Biomarker Endpoint',
        labs.title = 'Biomarker Timecourse',
        labs.caption = 'Ribbons represent Tukey hinges and whiskers')
```

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Ribbons represent Tukey hinges and whiskers