Biomarker analysis report

2017-08-29

Contents

1 The dataset

The dataset have 550 entries. In which 326 are in biomarker evaluable population (BEP).

- Endpoint of interest: Response
- Biomarker: KRAS.mutant
- Biomarker type: categorical

2 Representativeness: Selection Bias of Biomarker Population

In this section, we are trying to answer the question: *Are biomarker evaluable population representative of the full population population?*

Key baseline demographics and prognostic characteristics (including stratification variables and any variables with known prognostic effect) and efficacy outcomes should be summarized by treatment groups and compared between biomarker evaluable population (BEP) and the full population. These analyses are conducted to investigate any potential selection bias associated with the availability of the biomarker (e.g. we may not get enough tissue for patients whose tumor size is small. Therefore they may be exlcuded from BEP).

The key clinical biomarkers considered are:

```
clinical.vars.class
```

```
##           Sex           Age
## "categorical"     "numeric"
```

2.1 Check selection bias in terms of key clinical variables, between full population and BEP

```
kable(SummaryVars(data=input, trt=trt, subgroup=BEP, subgroup.indicator = BEP.indicator,
                  var=clinical.vars, var.class=clinical.vars.class))
```

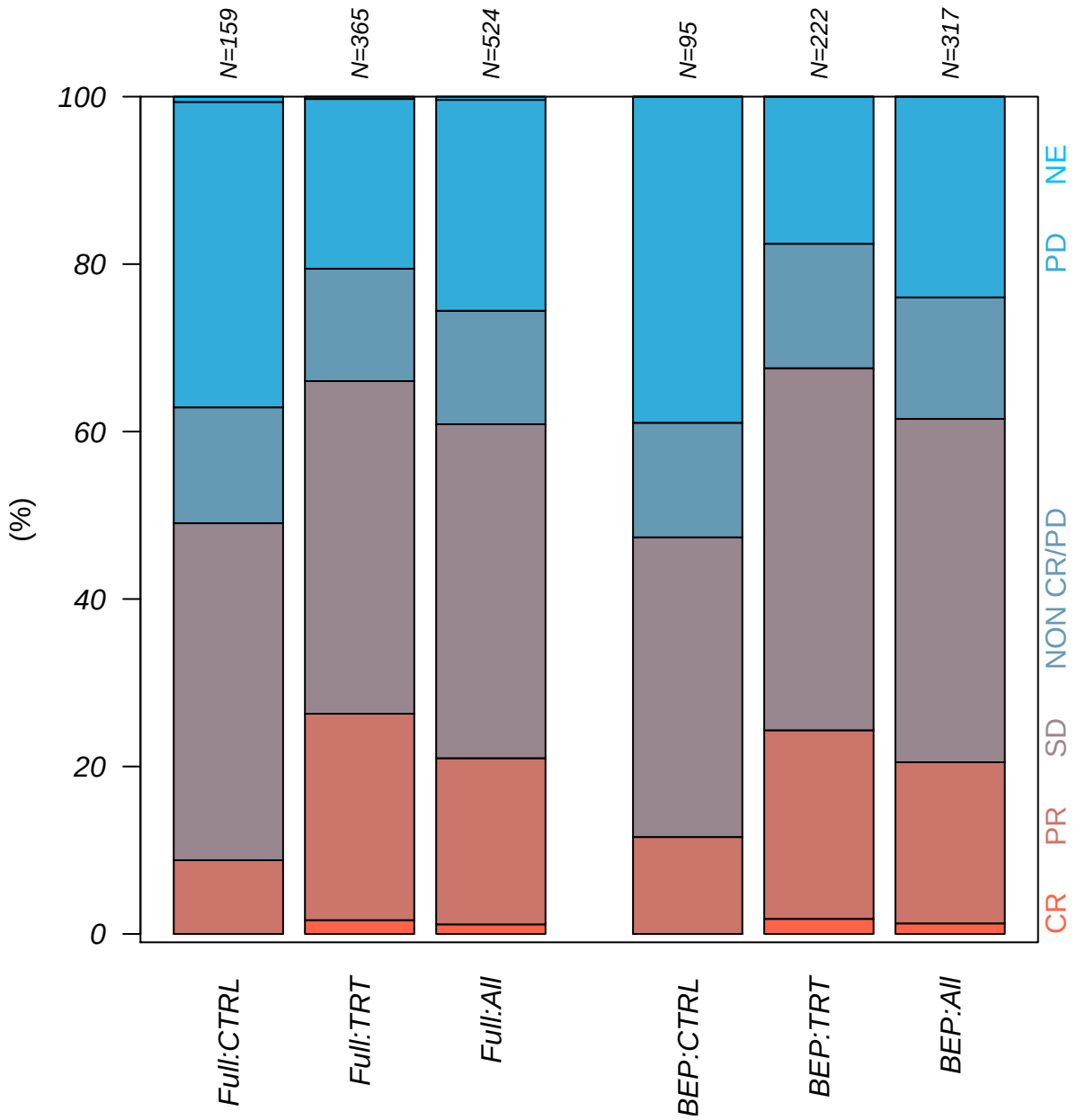
	All(CTRL)	BEP(CTRL)	All(TRT)	BEP(TRT)
Sex				
Total	182	103	368	223
NA's	0	0	0	0
F	89 (48.9%)	47 (45.63%)	184 (50%)	111 (49.78%)
M	93 (51.1%)	56 (54.37%)	184 (50%)	112 (50.22%)
Age				
N	182	103	368	223
Mean	52.54	52.93	54.03	54.27
Median	51.5	52	54	54
Min-Max	27...85	32...85	30...89	33...89
NA's	0	0	0	0

2.2 Check whether the clinical outcome in BEP is comparable to the full population

The following plot compares response outcome in BEP vs. the full population. The response category distribution is plotted for each arm. The BEP bars are expected to be comparable to those in full population.

```
Rsp.out <- PlotRspBar(data=input, outcome.var=outcome.var, binary=FALSE,
rsp.levels=rsp.levels, trt=trt, bep.indicator=BEP.indicator,
compare.bep.itt=TRUE, bep = BEP)
```

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




```
kable(Rsp.out$count,caption="count")
```

Table 2: count

	CR	PR	SD	NON CR/PD	PD	NE
Full:CTRL	0	14	64	22	58	1
Full:TRT	6	90	145	49	74	1
Full:All	6	104	209	71	132	2
BEP:CTRL	0	11	34	13	37	0
BEP:TRT	4	50	96	33	39	0
BEP:All	4	61	130	46	76	0

```
kable(round(Rsp.out$perc,2), caption="percentage")
```

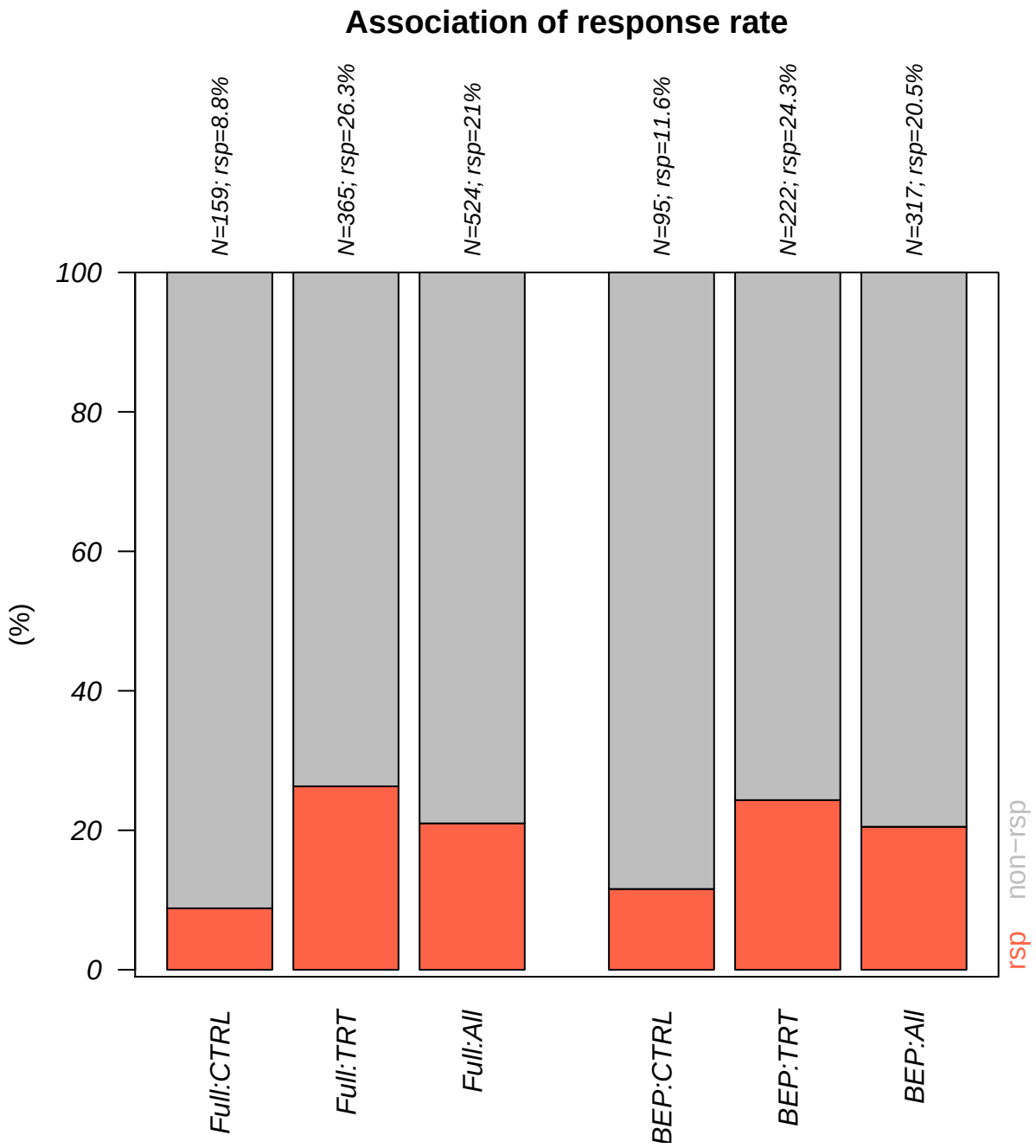
Table 3: percentage

	CR	PR	SD	NON CR/PD	PD	NE
Full:CTRL	0.00	0.09	0.40	0.14	0.36	0.01
Full:TRT	0.02	0.25	0.40	0.13	0.20	0.00
Full:All	0.01	0.20	0.40	0.14	0.25	0.00
BEP:CTRL	0.00	0.12	0.36	0.14	0.39	0.00
BEP:TRT	0.02	0.23	0.43	0.15	0.18	0.00
BEP:All	0.01	0.19	0.41	0.15	0.24	0.00

Summarize the response in two classes - rsp vs. non-rsp:

```
Rsp.out.2 <- PlotRspBar(data=input, outcome.var=outcome.var, binary=TRUE,
rsp.response = rsp.response,
rsp.nonresponse = rsp.nonresponse,rsp.name=rsp.name, trt=trt, bep.indicator=BEP.indicator,
compare.bep.itt=TRUE, bep = BEP)
```

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




```
kable(Rsp.out.2$count,caption="count")
```

Table 4: count

	rsp	non-rsp
Full:CTRL	14	145
Full:TRT	96	269
Full:All	110	414
BEP:CTRL	11	84
BEP:TRT	54	168
BEP:All	65	252

```
kable(round(Rsp.out.2$perc,2), caption="percentage")
```

Table 5: percentage

	rsp	non-rsp
Full:CTRL	0.09	0.91
Full:TRT	0.26	0.74
Full:All	0.21	0.79
BEP:CTRL	0.12	0.88
BEP:TRT	0.24	0.76
BEP:All	0.21	0.79

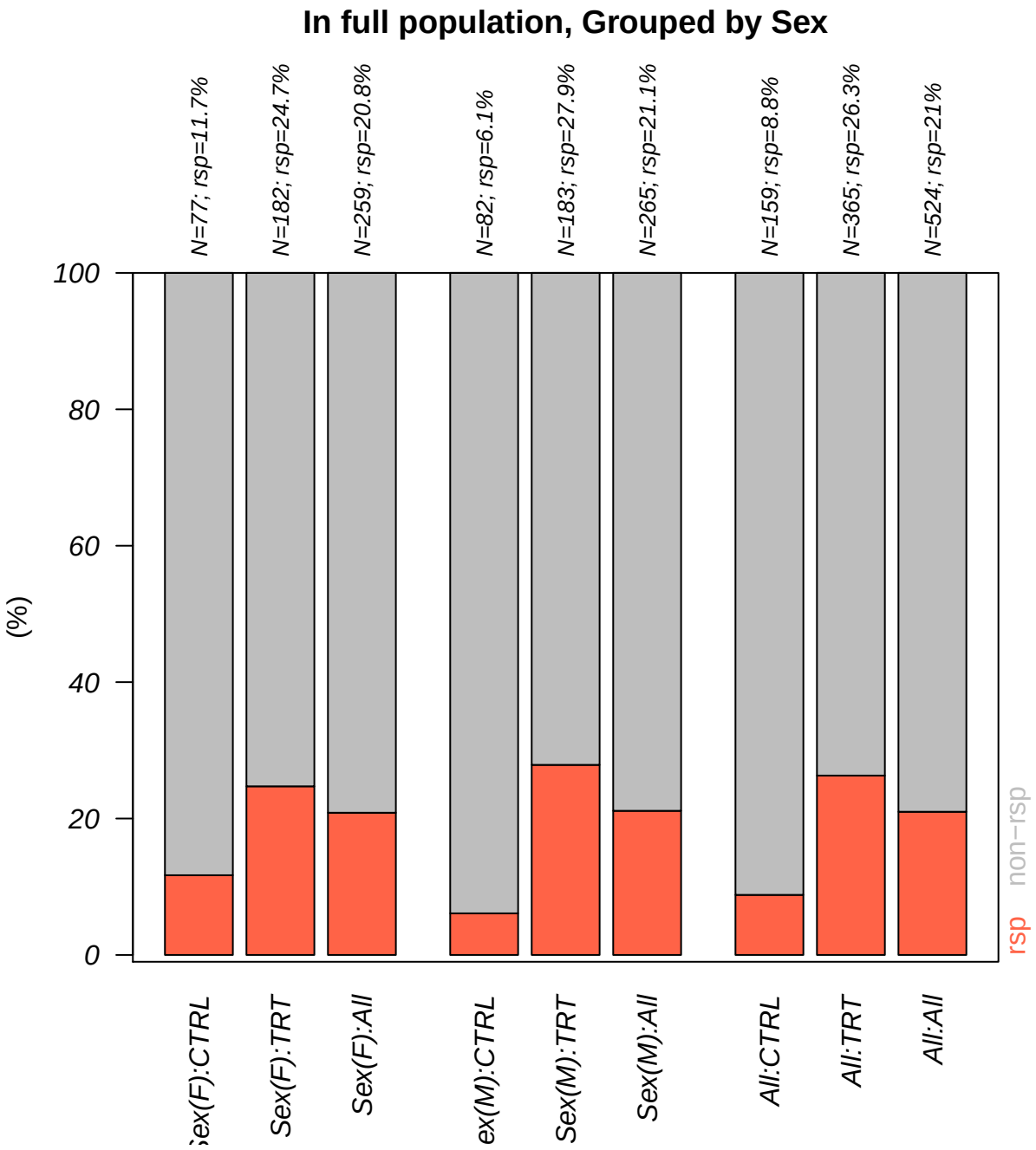
2.3 Examine whether the prognostic/predictive/null trend of key clinical variables holds in BEP

The following forest plot can be used to examine whether any of the key prognostic/predictive clinical variables still show prognostic/predictive trend in BEP:

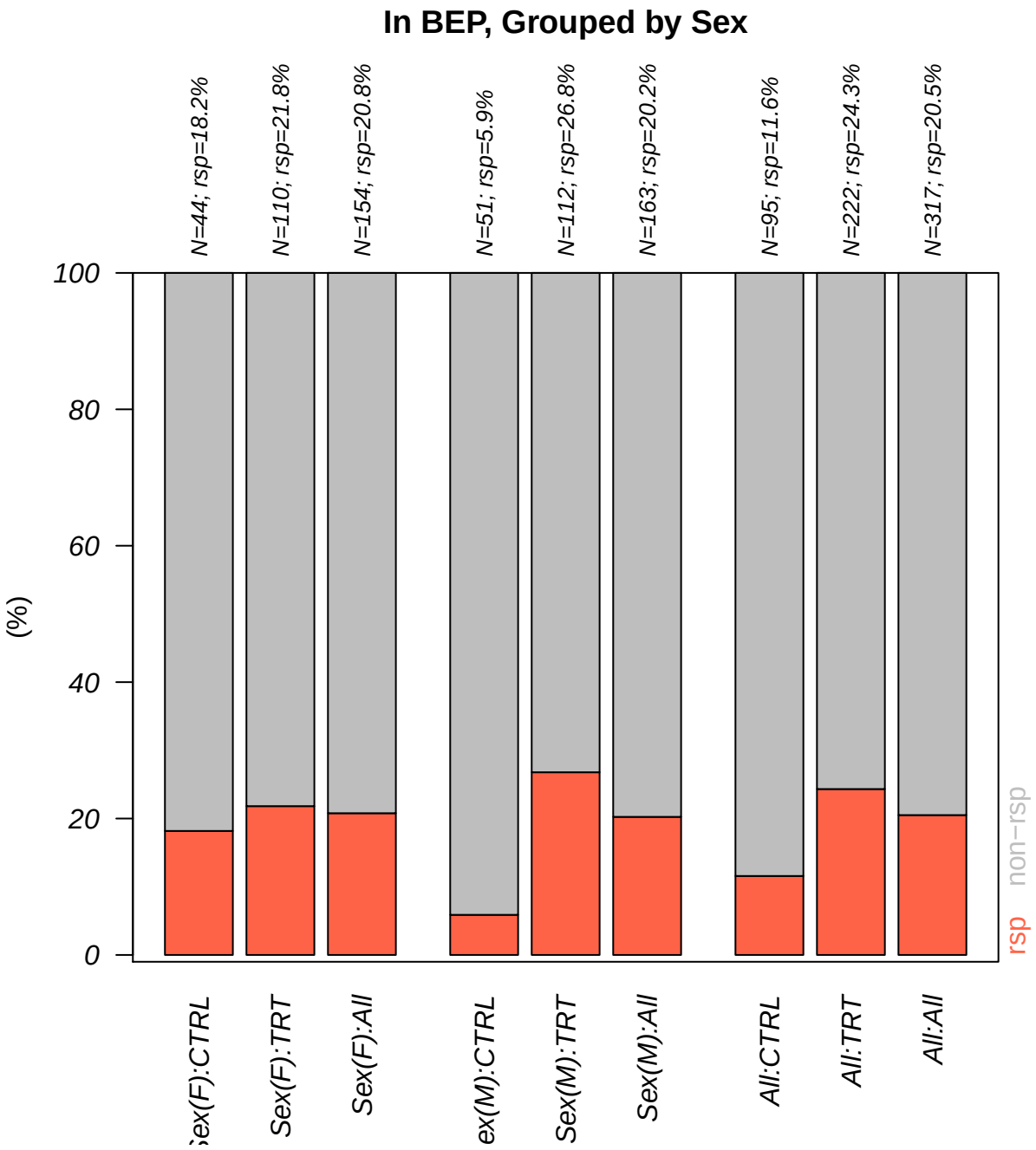
```
for(vv in clinical.vars.2){

  Rsp.out.tmp <- PlotRspBar(data=input, outcome.var=outcome.var, binary=TRUE,
  rsp.response = rsp.response,
  rsp.nonresponse = rsp.nonresponse,rsp.name=rsp.name, trt=trt,
  compare.var =TRUE,  var=vv, main=paste("In full population, Grouped by", vv))

  Rsp.out.tmp <- PlotRspBar(data=input.bep,
                            outcome.var=outcome.var, binary=TRUE,
  rsp.response = rsp.response,
  rsp.nonresponse = rsp.nonresponse,rsp.name=rsp.name, trt=trt,
  compare.var =TRUE, var=vv, main=paste("In BEP, Grouped by", vv))
}
```

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

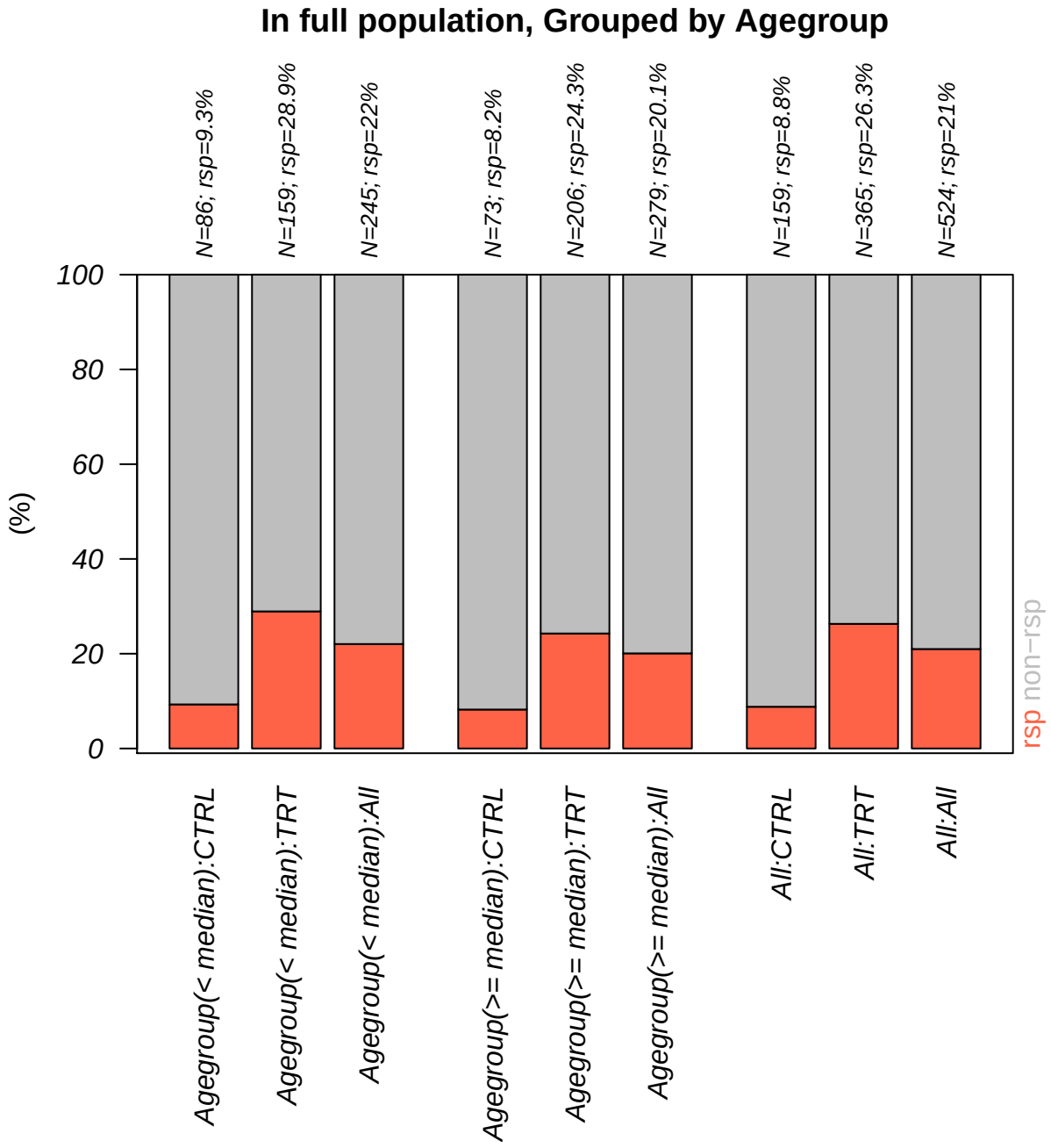
```
## entries with missing outcome.var are removed! 317 entries left
```

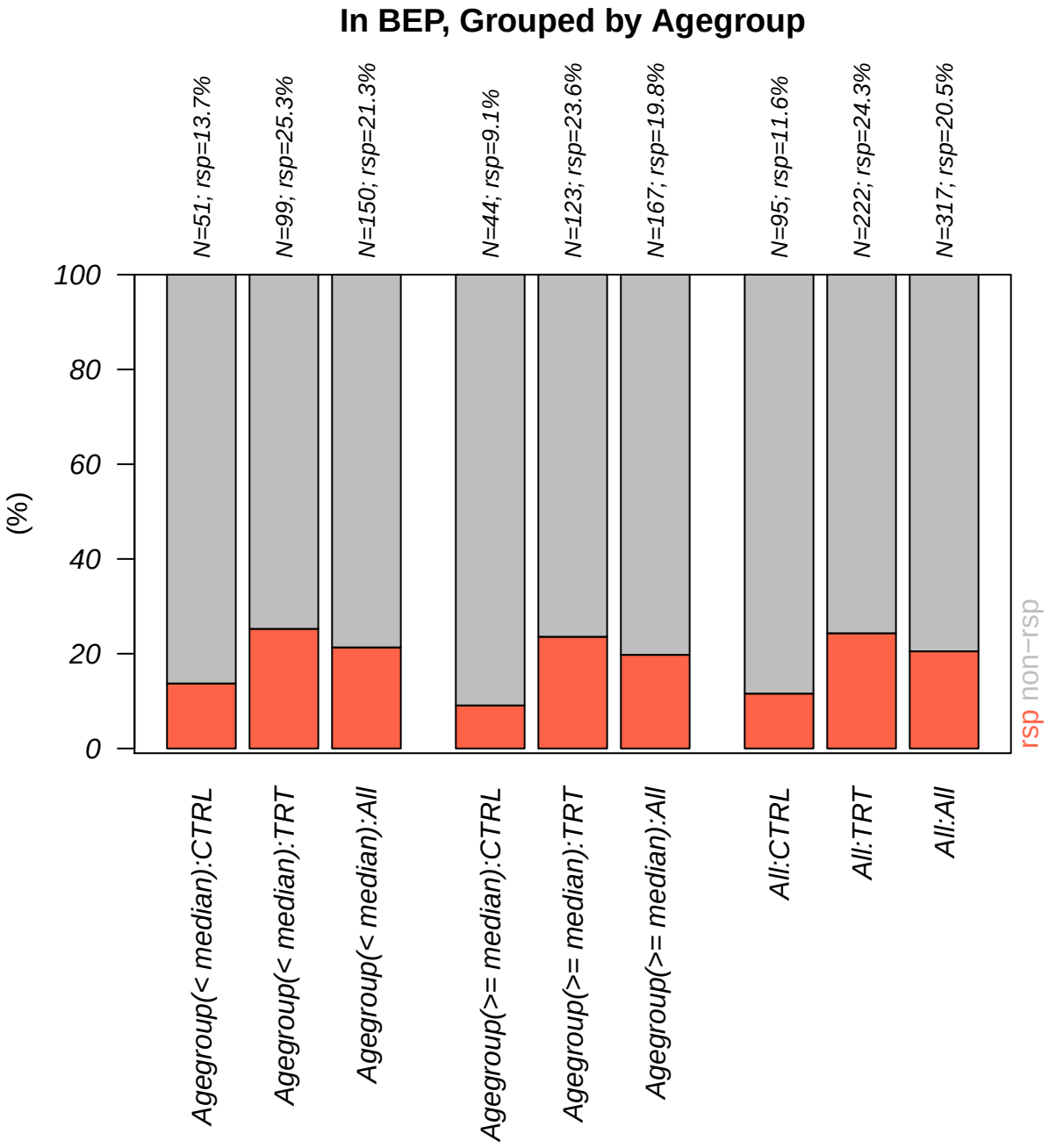



```
## entries with missing outcome.var are removed! 524 entries left
```




```
## entries with missing outcome.var are removed! 317 entries left
```


In full population, Grouped by Agegroup
N=86; rsp=9.3%
N=159; rsp=28.9%
N=245; rsp=22%
N=73; rsp=8.2%
N=206; rsp=24.3%
N=279; rsp=20.1%
N=159; rsp=8.8%
N=365; rsp=26.3%
N=524; rsp=21%
100
80
60
40
20
0
(%)
rsp
non−rsp
Agegroup(< median):CTRL
Agegroup(< median):TRT
Agegroup(< median):All
Agegroup(>= median):CTRL
Agegroup(>= median):TRT
Agegroup(>= median):All
All:CTRL
All:TRT
All:All



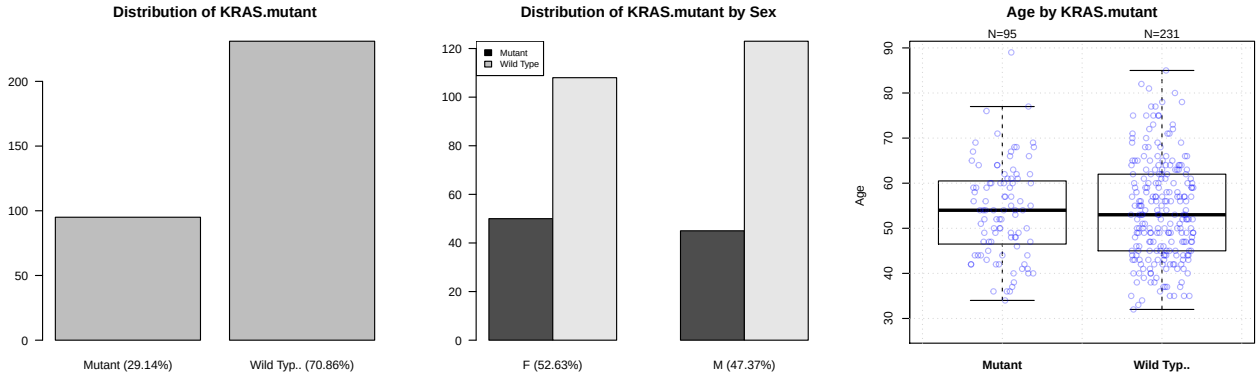
3 Biomarker property and its association to clinical variables

Relationship between the biomarker and key demographic and prognostic variables should also be investigated using bivariate plots. Prognostic property of the biomarker should also be assessed, by estimates of the clinical efficacy in the control arm.

3.1 Biomarker property and relationship to clinical variable

The following results show single variate plot for biomaker and bi-variate plots to investigate biomarker-clinical variable relationship.

```
PlotProperty(data=input, biomarker.var=bm, biomarker.class=bm.class,
             var=clinical.vars,
             var.class=clinical.vars.class,
             log2=FALSE, par.param = list(mfrow=c(2,3)))
```



3.2 Whether the biomarker shows within-arm effect

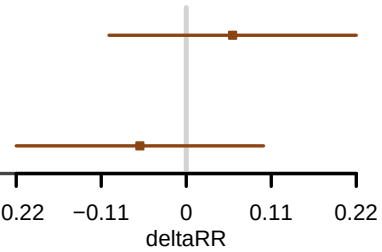
The following figures investigate whether the biomarker shows a within-arm effect:

```
input.ctrl <- subset(input, Arm==placebo.code) ## Data with only ctrl samples
res.multicut.ctrl <- PlotTabForestBiomarker(data=input.ctrl,
                                    outcome.class=outcome.class,
                                    outcome.var=outcome.var,
                                    var=bm,
                                    var.class=bm.class,
                                    percentile.cutoff=percentile.trycut,
                                    numerical.cutoff = numerical.trycut,
                                    rsp.response = rsp.response,
                                    rsp.nonresponse = rsp.nonresponse,
                                    main.prefix=placebo.code,
                                    greater=TRUE, less=FALSE,
                                    covariate=covariate, strata=strata)
```

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

## 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

## Warning in prop.test(c(r1, r2), c(n1, n2), conf.level = 1 - alpha,
## correct = fit.para[["prop.test.use.continuity.correction"]]): Chi-squared
## approximation may be incorrect

## Warning in prop.test(c(r1, r2), c(n1, n2), conf.level = 1 - alpha,
## correct = fit.para[["prop.test.use.continuity.correction"]]): Chi-squared
## approximation may be incorrect
```

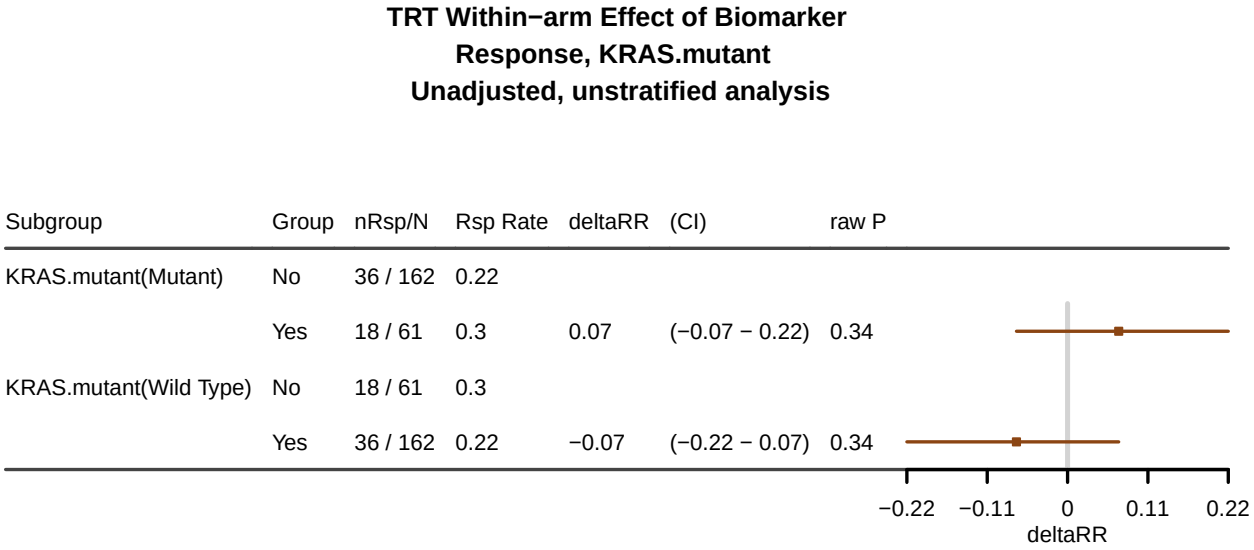
CTRL Within−arm Effect of Biomarker Response, KRAS.mutant Unadjusted, unstratified analysis

Subgroup	Group	nRsp/N	Rsp Rate	deltaRR	(CI)	raw P
KRAS.mutant(Mutant)	No	6 / 69	0.09			
	Yes	5 / 34	0.15	0.06	(−0.1 − 0.22)	0.56
KRAS.mutant(Wild Type)	No	5 / 34	0.15			
	Yes	6 / 69	0.09	−0.06	(−0.22 − 0.1)	0.56




```
input.trt <- subset(input, Arm==active.code) ## Data with only ctrl samples
res.multicut.trt <- PlotTabForestBiomarker(data=input.trt,
                                    outcome.class=outcome.class,
                                    outcome.var=outcome.var,
                                    var=bm,
                                    var.class=bm.class,
                                    percentile.cutoff=percentile.trycut,
                                    numerical.cutoff = numerical.trycut,
                                    rsp.response = rsp.response,
                                    rsp.nonresponse = rsp.nonresponse,
                                    main.prefix=active.code,
                                    greater=TRUE, less=FALSE,
                                    covariate=covariate, strata=strata)
```

```
## Covariate adjustment and stratification are not supported for binary outcome
## 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
## Warning in par(old.par): calling par(new=TRUE) with no plot
```



The forest plots above show within-arm response rate difference (delta) between biomarker subgroups. For a given arm, if the delta is not all around 0, it indicates that within this arm the biomarker has an association to the clinical outcome.

If similar trend is seen in both arms, it indicates that the biomarker may have a prognostic effect (the biomarker is able to identify patients with better/worse clinical outcome, regardless of treatment).

4 Biomarker subgroup analysis

4.1 Estimations within each subgroup

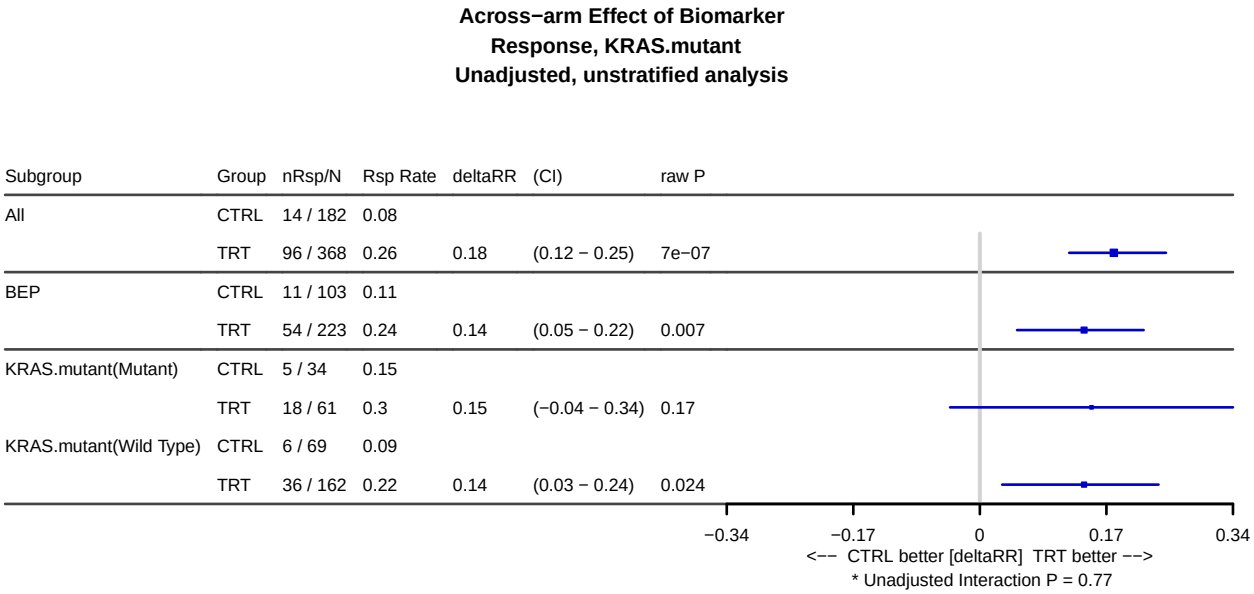
The following figure shows estimate of treatment effect in biomarker subgroups.

```
if(bm.class=="numeric"){
if(!is.null(numerical.finalcut)) levs <- paste0(c(">=","<"),numerical.finalcut)
if(is.null(numerical.finalcut)) {
  nm <- quantile(input.bep[[bm]],percentile.finalcut, 2) # default quantile type in forest plot functio
  numerical.finalcut <- round(nm,2) # default rounding decimal in forest plots
  levs <- paste0(c(">=","<"),percentile.finalcut*100,"%")
}

bm2 <- paste0(bm,"_Dx")
input[[bm2]] <- ifelse(input[[bm]] >= numerical.finalcut, levs[1],levs[2])
input[[bm2]]<- factor(input[[bm2]], levels=levs) # ">=" as Dx+
}

if(bm.class=="categorical") {
  bm2 <- bm
  levs <- unique(input[[bm2]])
}

res.2group <- PlotTabForestBiomarker(data=input,
                                     outcome.class=outcome.class,
                                     outcome.var=outcome.var,
                                     trt=trt,
                                     var=bm2,
```

```
                                    var.class="categorical",
                                    greater=TRUE, less=TRUE,
                                    show.itt=TRUE, show.bep=TRUE,
                                    covariate=covariate, strata=strata)
```

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

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

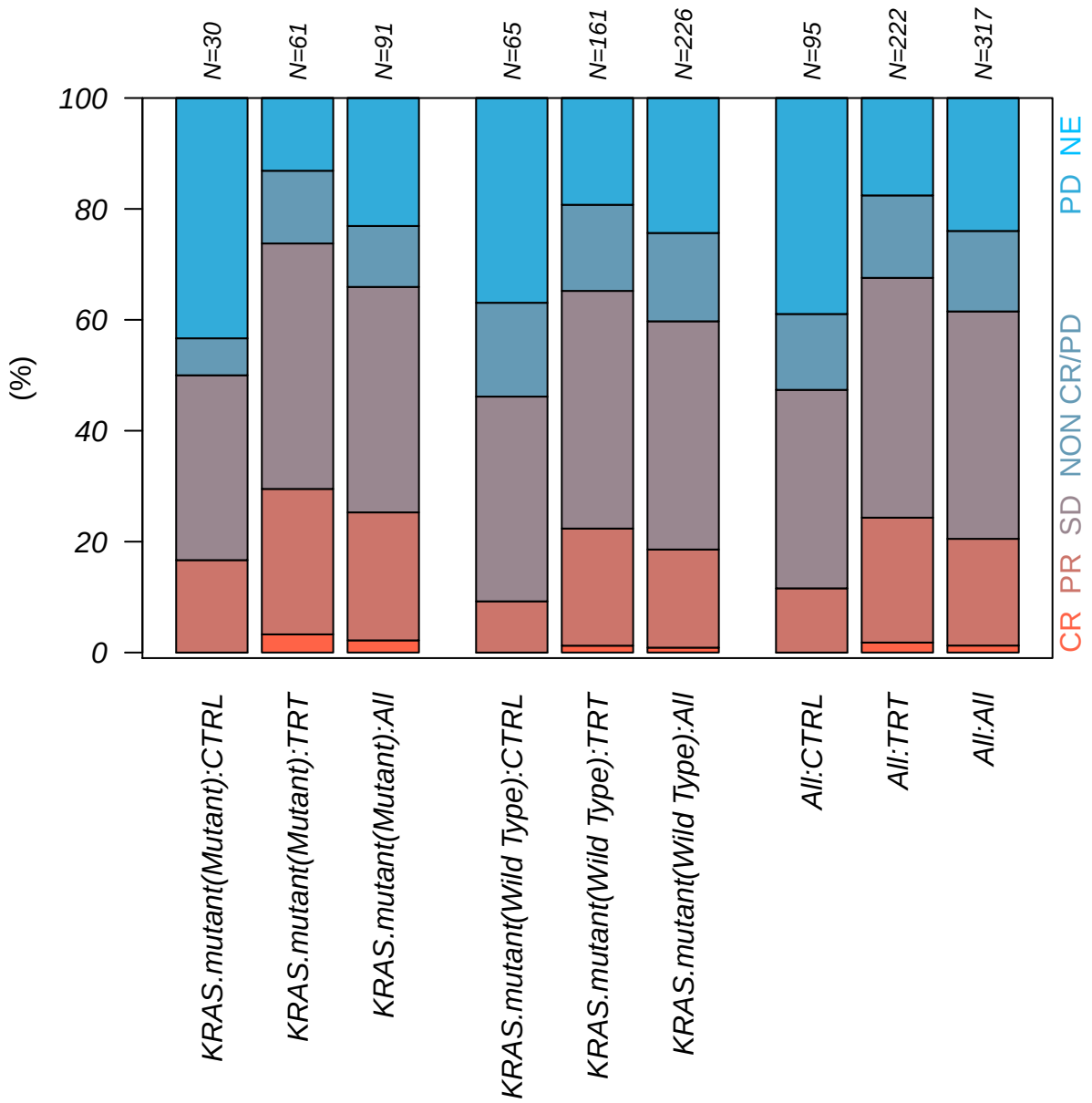


4.2 Subgroup analysis

The following figure show response category distributions of the biomarker subgroups:

```
Rsp.out <- PlotRspBar(data=input, outcome.var=outcome.var, binary=FALSE,
rsp.levels=rsp.levels, trt=trt, bep.indicator=BEP.indicator, var=bm2,
compare.var=TRUE, bep = BEP)
```

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




```
kable(Rsp.out$count,caption="count")
```

Table 6: count

	CR	PR	SD	NON CR/PD	PD	NE
KRAS.mutant(Mutant):CTRL	0	5	10	2	13	0
KRAS.mutant(Mutant):TRT	2	16	27	8	8	0
KRAS.mutant(Mutant):All	2	21	37	10	21	0
KRAS.mutant(Wild Type):CTRL	0	6	24	11	24	0
KRAS.mutant(Wild Type):TRT	2	34	69	25	31	0
KRAS.mutant(Wild Type):All	2	40	93	36	55	0
All:CTRL	0	11	34	13	37	0

	CR	PR	SD	NON CR/PD	PD	NE
All:TRT	4	50	96	33	39	0
All:All	4	61	130	46	76	0

```
kable(round(Rsp.out$perc,2), caption="percentage")
```

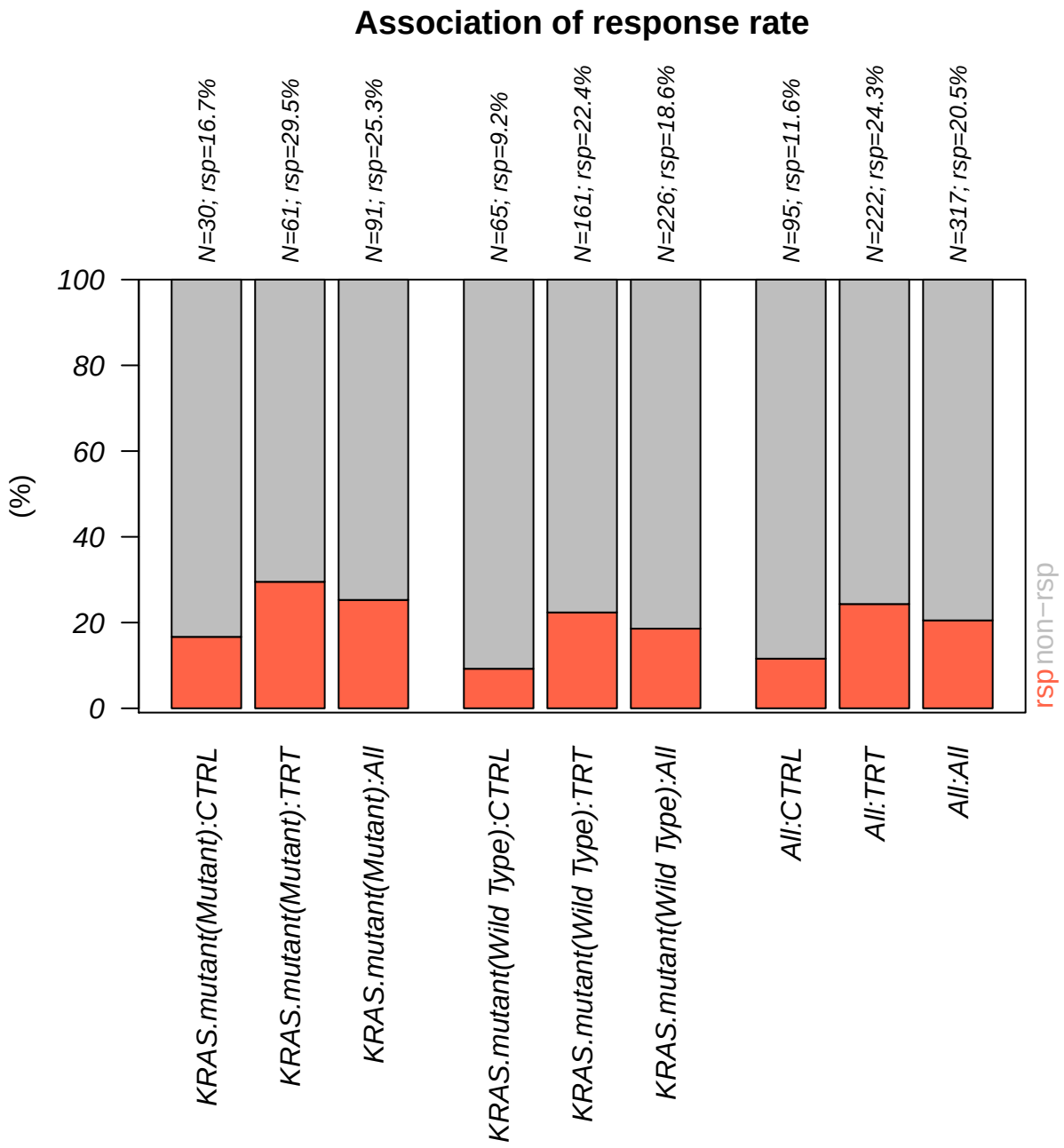
Table 7: percentage

	CR	PR	SD	NON CR/PD	PD	NE
KRAS.mutant(Mutant):CTRL	0.00	0.17	0.33	0.07	0.43	0
KRAS.mutant(Mutant):TRT	0.03	0.26	0.44	0.13	0.13	0
KRAS.mutant(Mutant):All	0.02	0.23	0.41	0.11	0.23	0
KRAS.mutant(Wild Type):CTRL	0.00	0.09	0.37	0.17	0.37	0
KRAS.mutant(Wild Type):TRT	0.01	0.21	0.43	0.16	0.19	0
KRAS.mutant(Wild Type):All	0.01	0.18	0.41	0.16	0.24	0
All:CTRL	0.00	0.12	0.36	0.14	0.39	0
All:TRT	0.02	0.23	0.43	0.15	0.18	0
All:All	0.01	0.19	0.41	0.15	0.24	0

Summarize the response in two classes - rsp vs. non-rsp:

```
Rsp.out.2 <- PlotRspBar(data=input, outcome.var=outcome.var, binary=TRUE,
rsp.response = rsp.response,
rsp.nonresponse = rsp.nonresponse,rsp.name=rsp.name, trt=trt, bep.indicator=BEP.indicator,
var=bm2, compare.var=TRUE, bep = BEP)
```

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




```
kable(Rsp.out.2$count,caption="count")
```

Table 8: count

	rsp	non-rsp
KRAS.mutant(Mutant):CTRL	5	25
KRAS.mutant(Mutant):TRT	18	43
KRAS.mutant(Mutant):All	23	68
KRAS.mutant(Wild Type):CTRL	6	59
KRAS.mutant(Wild Type):TRT	36	125
KRAS.mutant(Wild Type):All	42	184
All:CTRL	11	84
All:TRT	54	168

	rsp	non-rsp
All:All	65	252

```
kable(round(Rsp.out.2$perc,2), caption="percentage")
```

Table 9: percentage

	rsp	non-rsp
KRAS.mutant(Mutant):CTRL	0.17	0.83
KRAS.mutant(Mutant):TRT	0.30	0.70
KRAS.mutant(Mutant):All	0.25	0.75
KRAS.mutant(Wild Type):CTRL	0.09	0.91
KRAS.mutant(Wild Type):TRT	0.22	0.78
KRAS.mutant(Wild Type):All	0.19	0.81
All:CTRL	0.12	0.88
All:TRT	0.24	0.76
All:All	0.21	0.79

4.3 Check whether biomarker subgroup is confounded with key clinical variables

The following table checks whether the biomarker subgroup is confounded with clinical variables. Here we check whether the clinical variable distribution is comparable across biomarker subgroups.

```
input.bep <- input[which(input[[BEP]]==BEP.indicator),]


kable(
SummaryVars(data=input.bep,trt=trt, subgroup=bm2, var=clinical.vars,
       var.class=clinical.vars.class, subgroup.indicator=levs[1],compare.subgroup=TRUE)
)
```

	KRAS.mutant_Mutant(CTRL)	KRAS.mutant_Wild Type(CTRL)	KRAS.mutant_Mutant(TRT)	KRAS.mutant_Wild Type(TRT)
Sex				
Total	34	69	61	162
NA's	0	0	0	0
F	15 (44.12%)	32 (46.38%)	35 (57.38%)	76 (46.91%)
M	19 (55.88%)	37 (53.62%)	26 (42.62%)	86 (53.09%)
Age				
N	34	69	61	162
Mean	51.88	53.45	54.92	54.03
Median	52	52	54	53
Min-Max	36...77	32...85	34...89	33...82
NA's	0	0	0	0