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: Lab_ontrt
- 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 continuous 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.

```
par(mfrow=c(1,2))
BoxPlot(obj=input, form=as.formula(paste(outcome.var,"~",trt)),
        XaxisTab=list(font=2, col="darkblue", cex=1.25),
        Title=list(main="Full population"), mar=c(5,5,5,1))
BoxPlot(obj=input.bep, form=as.formula(paste(outcome.var,"~",trt)),
        XaxisTab=list(font=2, col="darkblue", cex=1.25),
        Title=list(main="BEP"), mar=c(5,5,5,1))
```
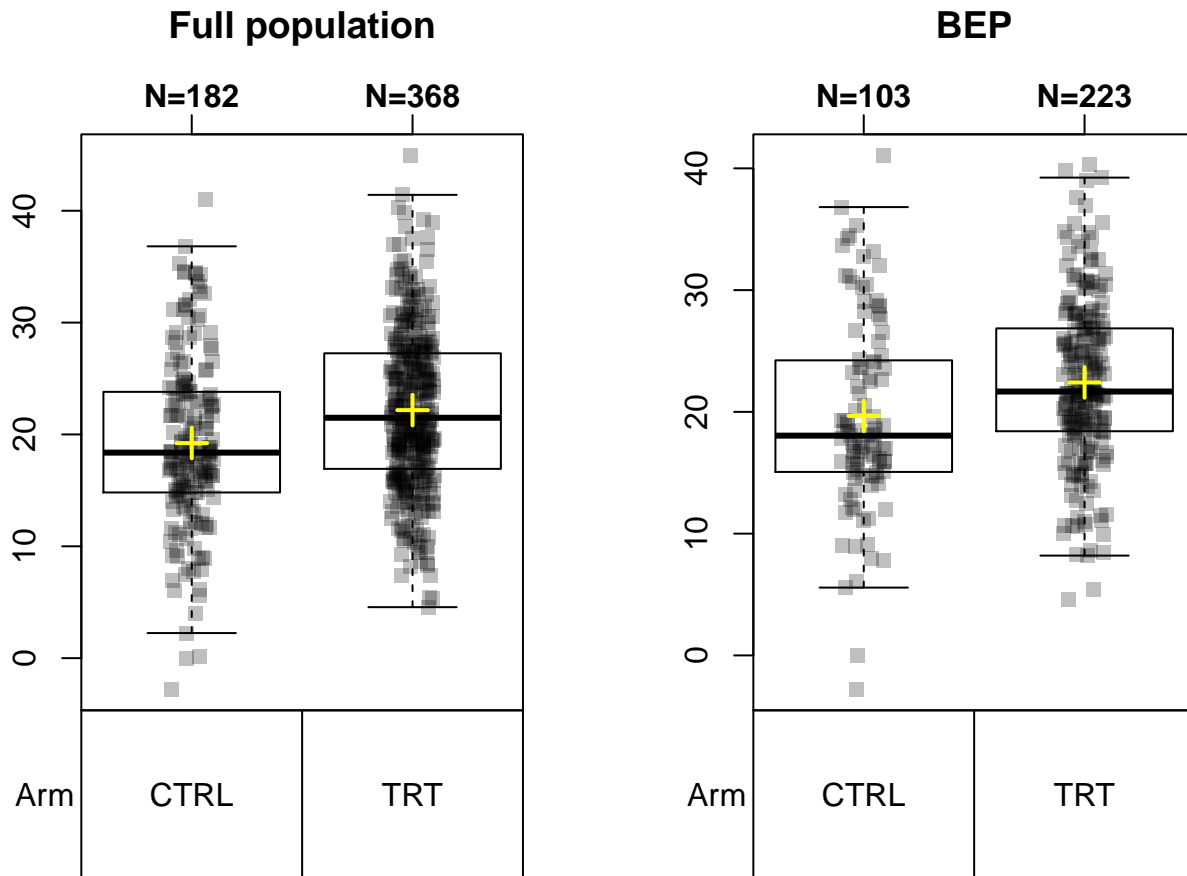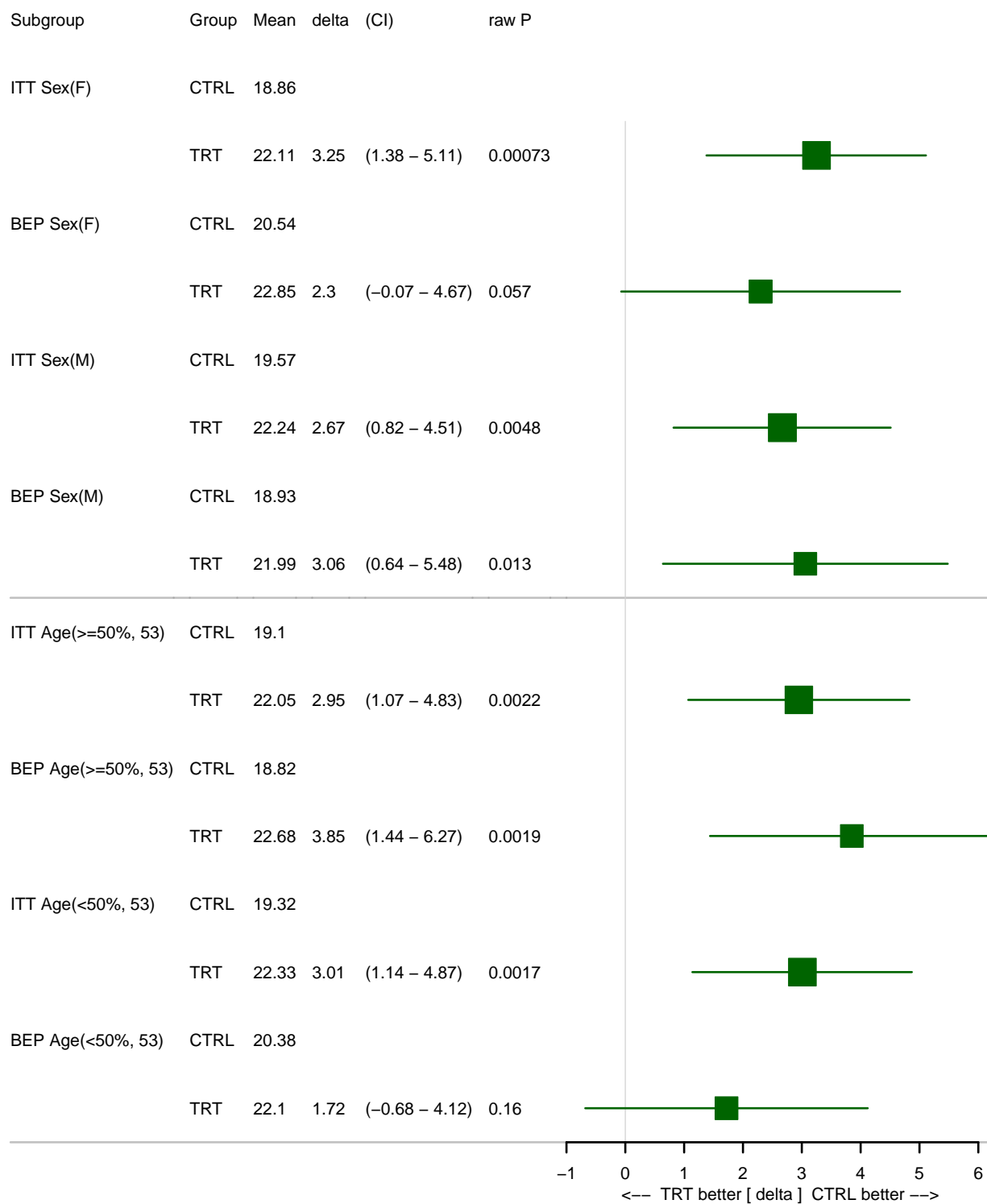
2.3 Examine whether the prognostic/predictive/null trend of key clinical variables holds in BEP

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:

```
forest.bep <- PlotTabForestMulti(data=input,
                outcome.class=outcome.class,
                outcome.var=outcome.var,
                trt=trt,
                var=clinical.vars,
                var.class=clinical.vars.class,
                bep=BEP,bep.indicator=BEP.indicator,
                compare.bep.itt=TRUE
                 )
```

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

Across arm, Compare BEP vs. All
Lab_ontrt
Unadjusted, unstratified analysis

Subgroup	Group	Mean	delta	(CI)	raw P
ITT Sex(F)	CTRL	18.86			
	TRT	22.11	3.25	(1.38 – 5.11)	0.00073
BEP Sex(F)	CTRL	20.54			
	TRT	22.85	2.3	(−0.07 – 4.67)	0.057
ITT Sex(M)	CTRL	19.57			
	TRT	22.24	2.67	(0.82 – 4.51)	0.0048
BEP Sex(M)	CTRL	18.93			
	TRT	21.99	3.06	(0.64 – 5.48)	0.013
ITT Age(>=50%, 53)	CTRL	19.1			
	TRT	22.05	2.95	(1.07 – 4.83)	0.0022
BEP Age(>=50%, 53)	CTRL	18.82			
	TRT	22.68	3.85	(1.44 – 6.27)	0.0019
ITT Age(<50%, 53)	CTRL	19.32			
	TRT	22.33	3.01	(1.14 – 4.87)	0.0017
BEP Age(<50%, 53)	CTRL	20.38			
	TRT	22.1	1.72	(−0.68 – 4.12)	0.16

−1   0   1   2   3   4   5   6
<−− TRT better [delta] CTRL better −−>
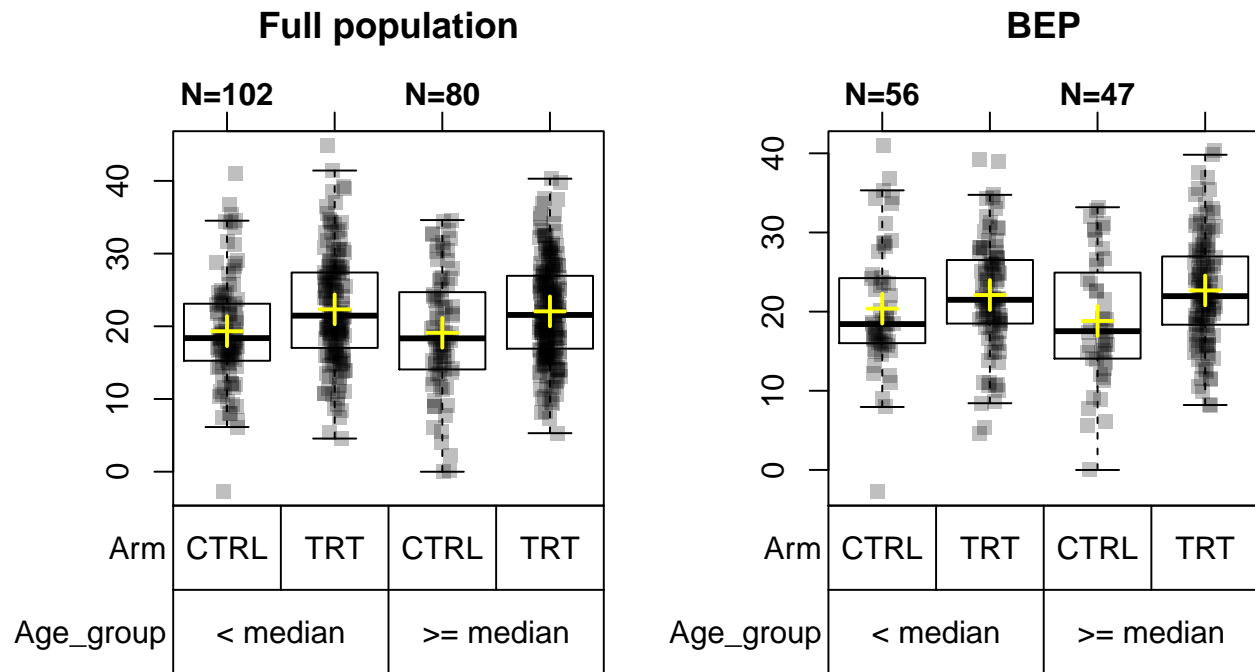
```
for(i in clinical.vars.2){
par(mfrow=c(1,2))
BoxPlot(obj=input, form=as.formula(paste(outcome.var,"~",trt,":",i)),
        XaxisTab=list(font=2, col="darkblue", cex=1.25),
        Title=list(main="Full population"), mar=c(5,5,5,1))
BoxPlot(obj=input.bep, form=as.formula(paste(outcome.var,"~",trt,":",i)),
        XaxisTab=list(font=2, col="darkblue", cex=1.25),
        Title=list(main="BEP"), mar=c(5,5,5,1))
print("")
}
```
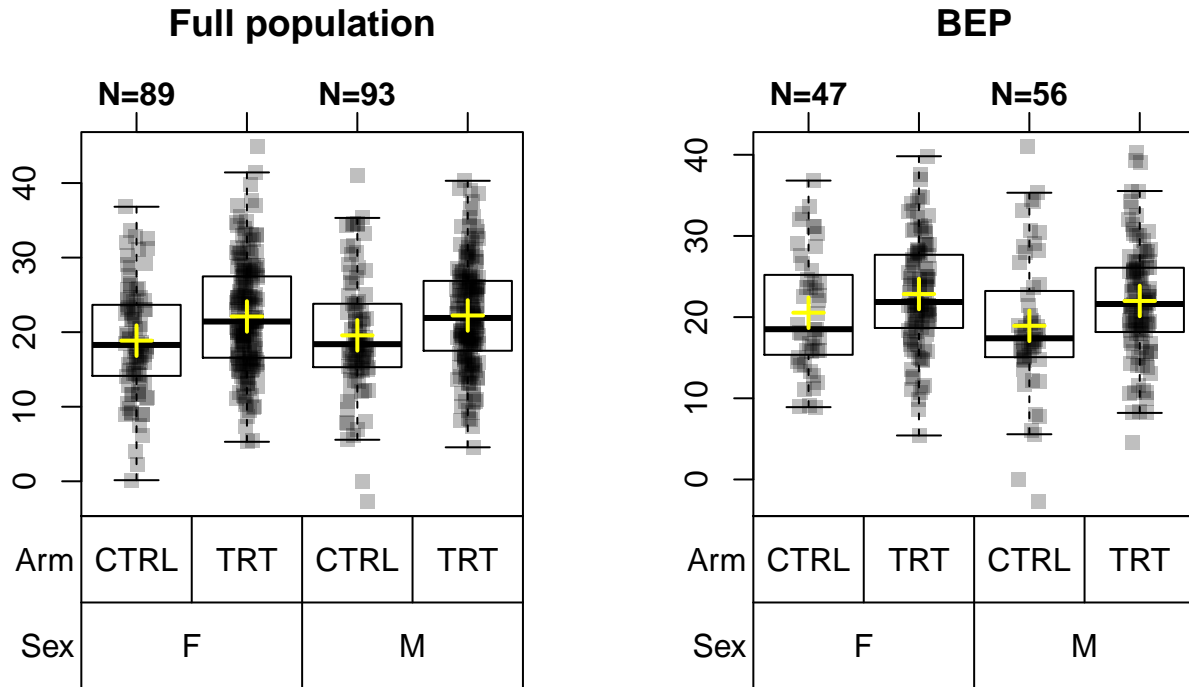


```
## [1] ""
```

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

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)))
```
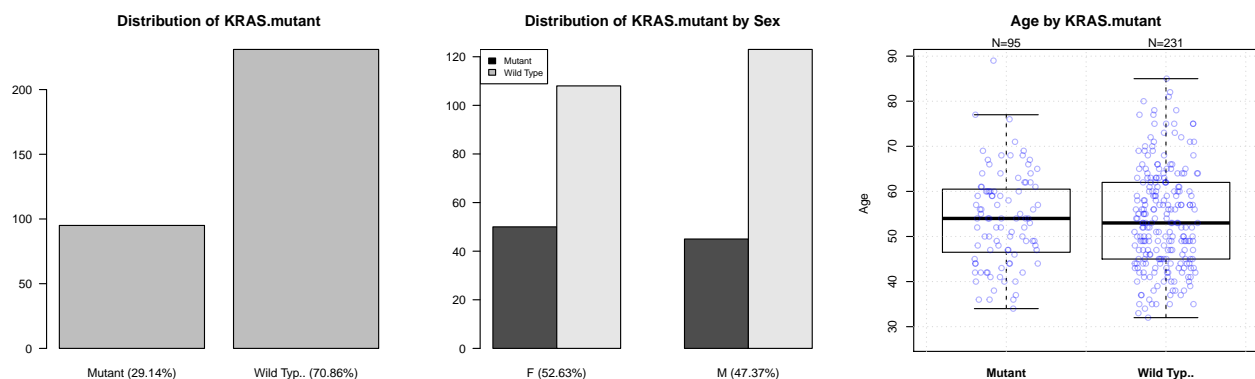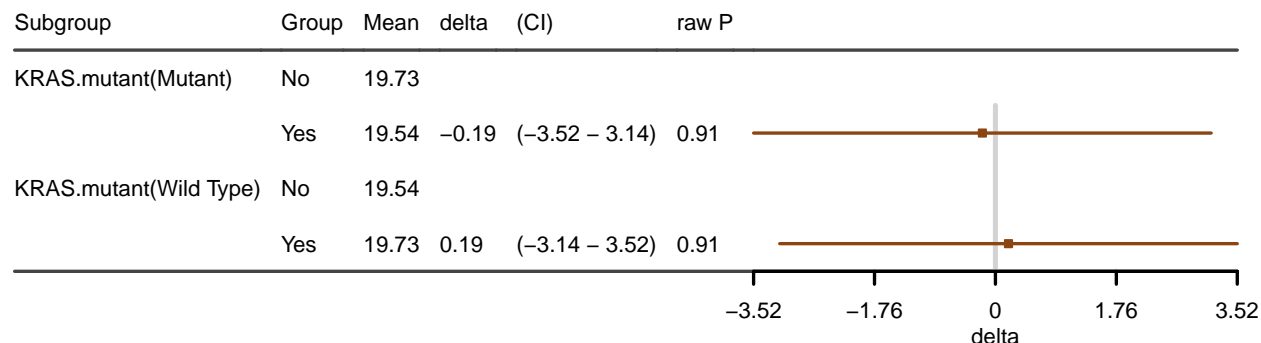
3.2 Whether the biomarker shows within-arm effect

The following figures investigate whether the biomarker shows a within-arm effect (e.g. patients in one biomarker subgroup tend to have better clinical outcome):

```
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)
```

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

CTRL Within–arm Effect of Biomarker
Lab_ontrt, KRAS.mutant
Unadjusted, unstratified analysis

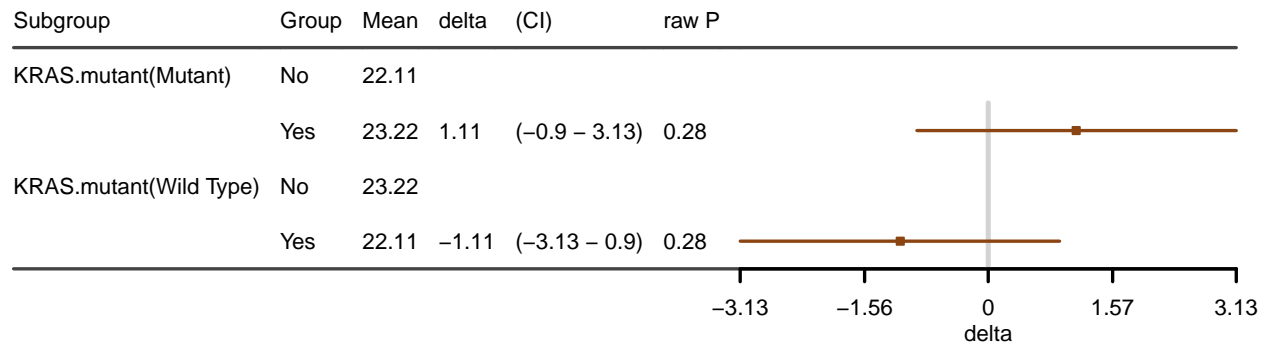| Subgroup	Group	Mean	delta	(CI)	raw P
KRAS.mutant(Mutant)	No	19.73			
	Yes	19.54	−0.19	(−3.52 – 3.14)	0.91
KRAS.mutant(Wild Type)	No	19.54			
	Yes	19.73	0.19	(−3.14 – 3.52)	0.91


```
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)
```

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

TRT Within–arm Effect of Biomarker
Lab_ontrt, KRAS.mutant
Unadjusted, unstratified analysis

Subgroup	Group	Mean	delta	(CI)	raw P
KRAS.mutant(Mutant)	No	22.11			
	Yes	23.22	1.11	(−0.9 – 3.13)	0.28
KRAS.mutant(Wild Type)	No	23.22			
	Yes	22.11	−1.11	(−3.13 – 0.9)	0.28

The forest plots above show within-arm mean difference (delta) across 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)
```
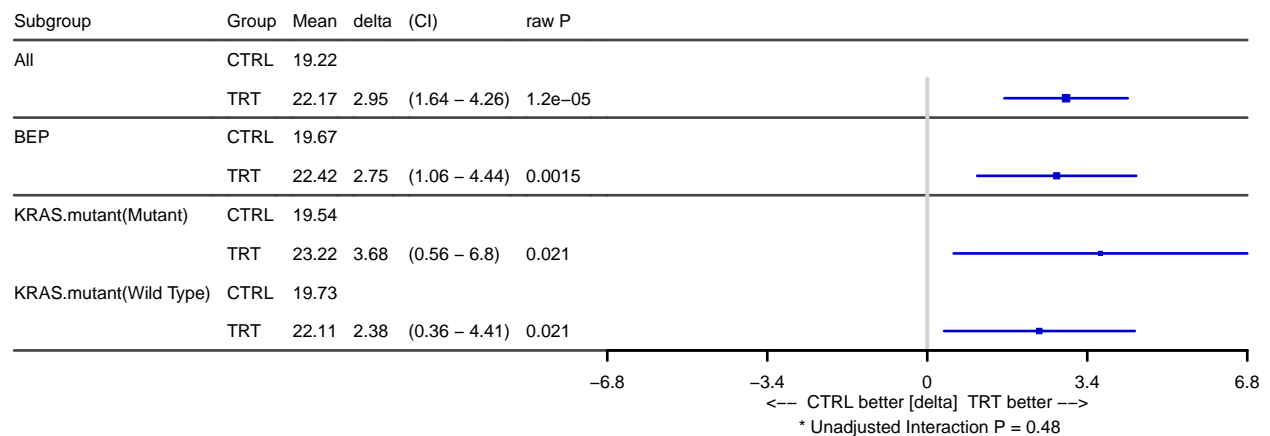
```
## Stratification is not supported for continuous outcome
```

```
## 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 ––>
                  * Unadjusted Interaction P = 0.48
```

4.2 Subgroup analysis

The following figure show distribution of the continuous endpoint within the biomarker subgroups:

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


BoxPlot(obj=input.bep, form=as.formula(paste(outcome.var,"~",trt,":",bm2)),
        XaxisTab=list(font=2, col="darkblue", cex=1.25),
        Title=list(main="BEP: biomarker subgroups"),
        mar=c(5,8,5,1))
```

BEP: biomarker subgroups

Arm	CTRL	TRT	CTRL	TRT
KRAS.mutant	Mutant		Wild Type	
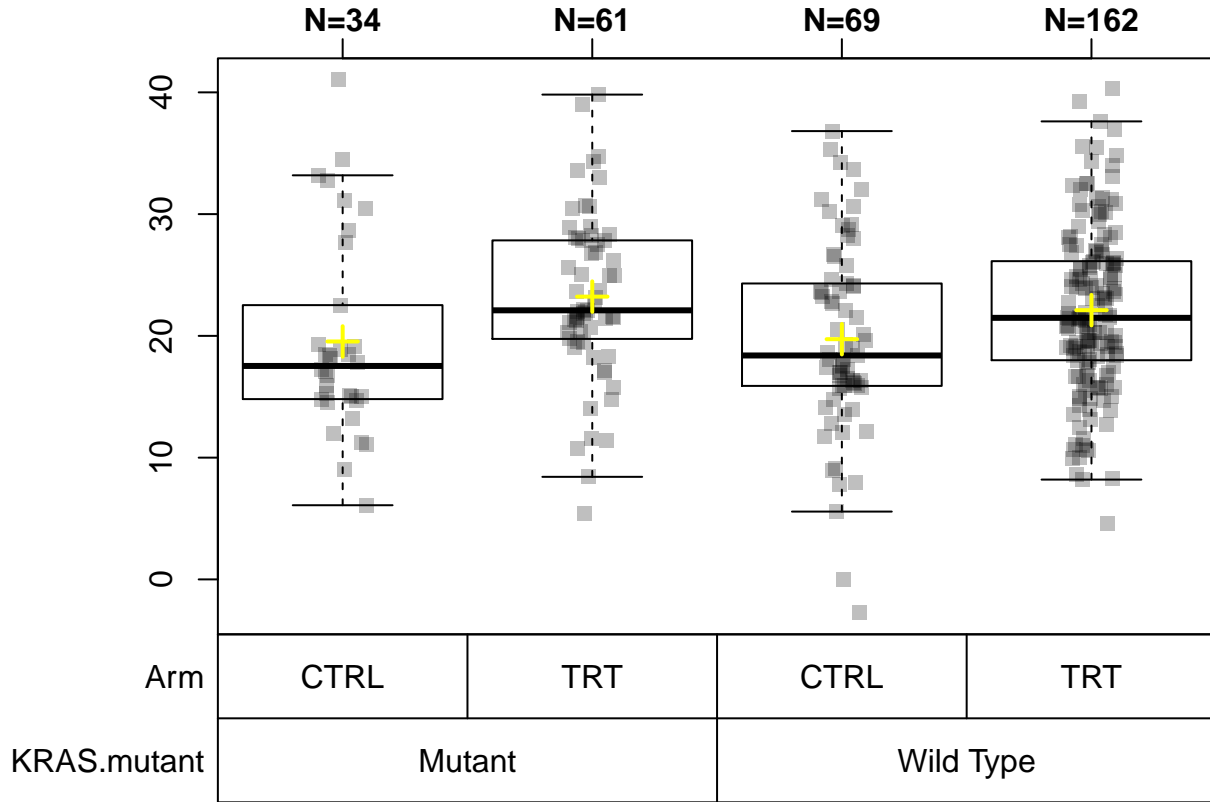
4.3 Check whether biomarker subgroup is confounded with key clinical variables

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

```
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