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: PFS
- 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

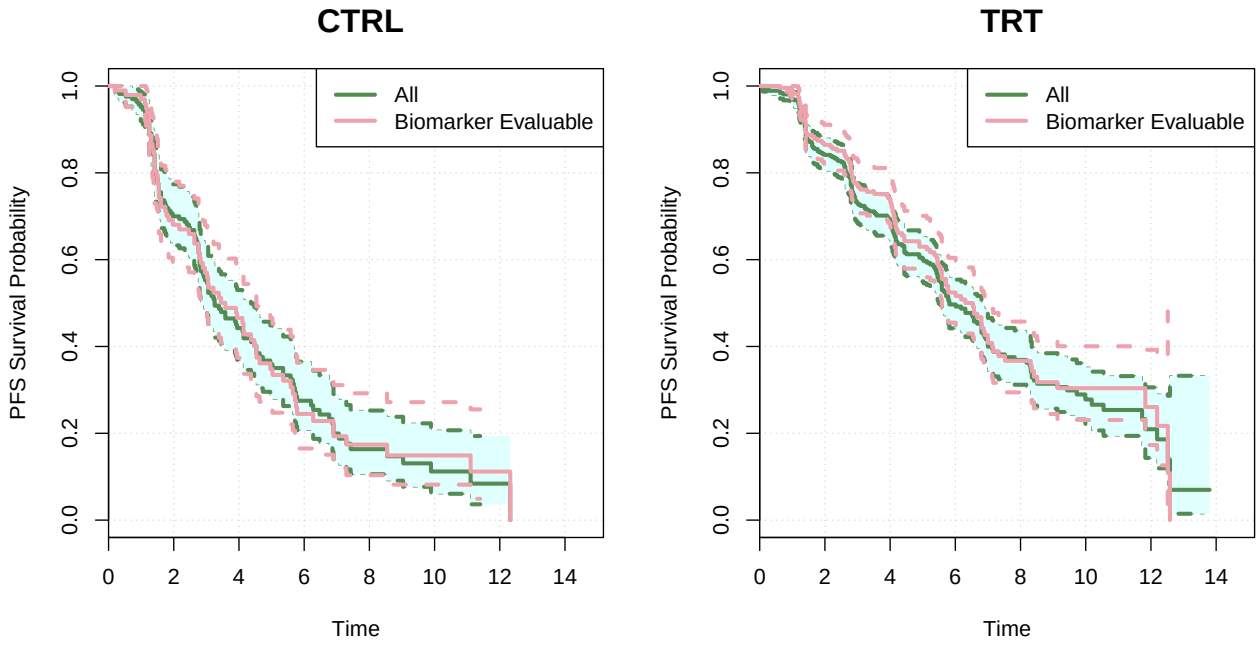
```
kable(SummaryVars(data=input, trt=trt, subgroup=BEP, subgroup.indicator = BEP.indicator, var=clinical.va
```

	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 survival outcome in BEP vs. the full population. The KM curve and 95% CI are plotted for each arm. The BEP KM curve is expected to be within the full population confidence bands.

```
CompareKM(data=input,tte=outcome.var[1], cen=outcome.var[2],trt=trt, bep=BEP, bep.indicator = BEP.indica
```



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

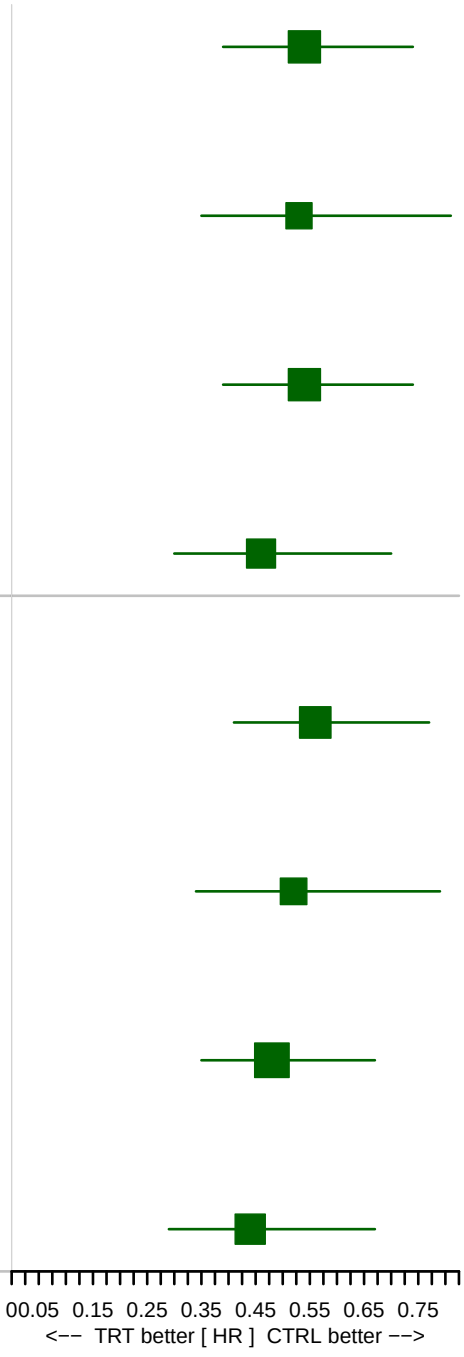
The following forest plot can be used to examine whether any of the key prognostic/predictive clinical variables still show prognostic/predictive trend in BEP:

```
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
                   )
```

```
## Some patients have missing outcome. Exclude these patients from ITT.
## Some patients have missing outcome. Exclude these patients from ITT.
## Some patients have missing outcome. Exclude these patients from ITT.
## Some patients have missing outcome. Exclude these patients from ITT.
```

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	33 / 47	4.11			
	TRT	64 / 111	5.59	0.53	(0.35 − 0.81)	0.0037
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
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
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



2.4 Compare treatment effect estimation in full population and in BEP, adjusted for key clinical variables

The following analyses show summary statistic to look at the trt/ctrl (target/reference) HR in full population and trt/ctrl HR in BEP. Both unadjusted and adjusted analyses are performed

```
kable(
  CoxTab(data=input, tte=outcome.var[1], cens=outcome.var[2], var=trt,
       var.class="categorical"),
caption="full population, unadjusted"
)
```

Table 2: full population, unadjusted

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Arm (TRT/CTRL)	0.54	0.43	0.67	7.8e-08	368	182

```
kable(
  CoxTab(data=input, tte=outcome.var[1], cens=outcome.var[2], var=c(trt, clinical.vars), var.class=c("ca
caption="full population, adjusted for clinical variables"
)
```

Table 3: full population, adjusted for clinical variables

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Arm (TRT/CTRL)	0.53	0.42	0.66	4.1e-08	368	182
Sex (M/F)	0.9	0.72	1.12	0.36	277	273
Age	1.01	1	1.02	0.079		

```
kable(
  CoxTab(data=input.bep, tte=outcome.var[1], cens=outcome.var[2], var=trt,
       var.class="categorical"),
caption="BEP, unadjusted"
)
```

Table 4: BEP, unadjusted

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Arm (TRT/CTRL)	0.5	0.37	0.66	2.8e-06	223	103

```
kable(
  CoxTab(data=input.bep, tte=outcome.var[1], cens=outcome.var[2], var=c(trt, clinical.vars), var.class=c
caption="BEP, adjusted for clinical variables"
)
```

Table 5: BEP, adjusted for clinical variables

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Arm (TRT/CTRL)	0.49	0.36	0.65	1.7e-06	223	103
Sex (M/F)	0.83	0.62	1.1	0.19	168	158

	HR	CI.low	CI.high	p-value	n.trt	n.ref
Age	1.01	0.99	1.02	0.37		

If any selection bias is suspected, you may consider to stratify for the imbalanced factor in downstream analysis (e.g. unstratified analysis as primary analysis and stratified analysis as sensitivity analysis).

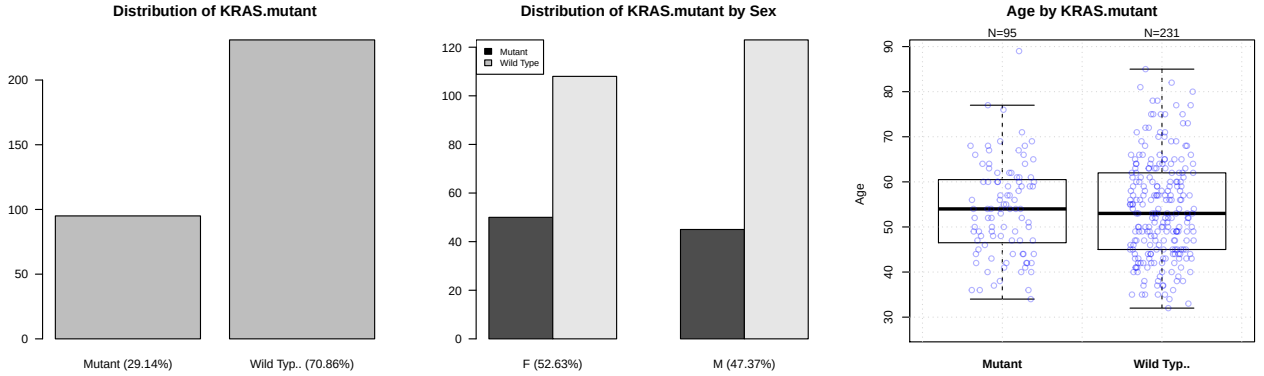
3 Biomarker property and its association to clinical variables

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

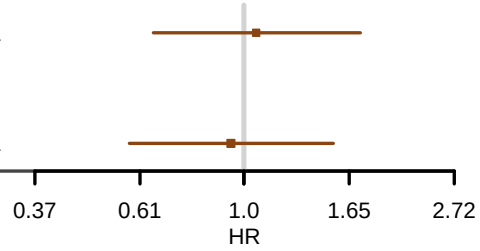
The following figures investigate whether the biomarker shows a within-arm effect (e.g. patients within one biomarker subgroup tend to have better clinical outcome):

```
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,
                                main.prefix=placebo.code,
                                greater=TRUE, less=FALSE,
                                covariate=covariate, strata=strata)
```

```
## Some patients have missing outcome. Exclude these patients from ITT.
## 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
```

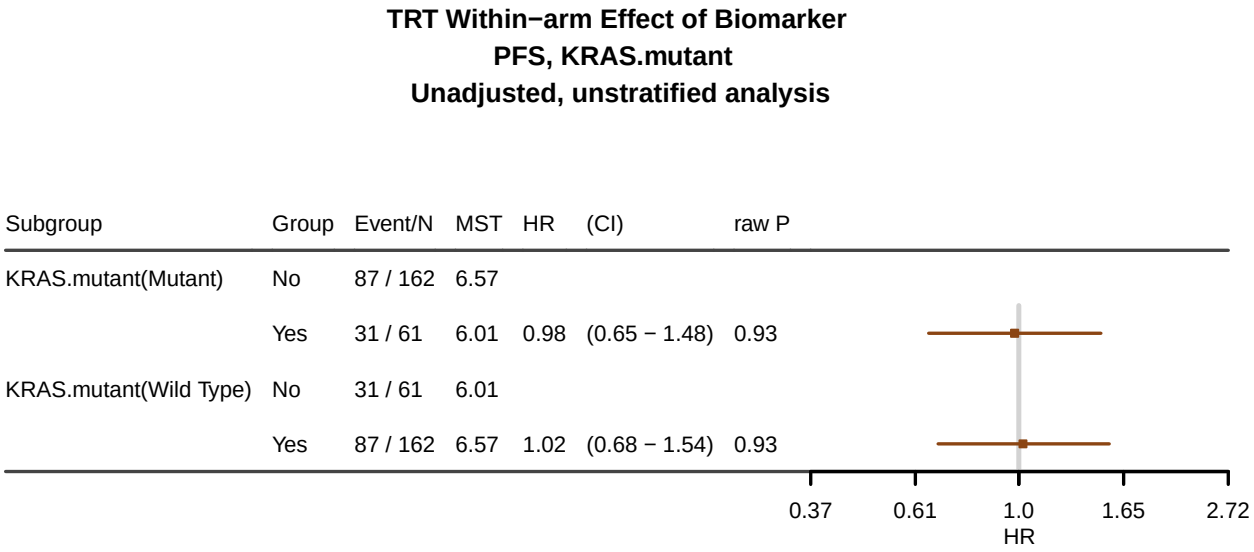
CTRL Within−arm Effect of Biomarker
PFS, KRAS.mutant
Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
KRAS.mutant(Mutant)	No	47 / 69	3.94			
	Yes	26 / 34	3.22	1.06	(0.65 − 1.74)	0.81
KRAS.mutant(Wild Type)	No	26 / 34	3.22			
	Yes	47 / 69	3.94	0.94	(0.58 − 1.53)	0.81




```
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,
                                  main.prefix=active.code,
                                  greater=TRUE, less=FALSE,
                                  covariate=covariate, strata=strata)
```

```
## Some patients have missing outcome. Exclude these patients from ITT.
## 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 HR across biomarker subgroups. For a given arm, if the HR is not all around 1, 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

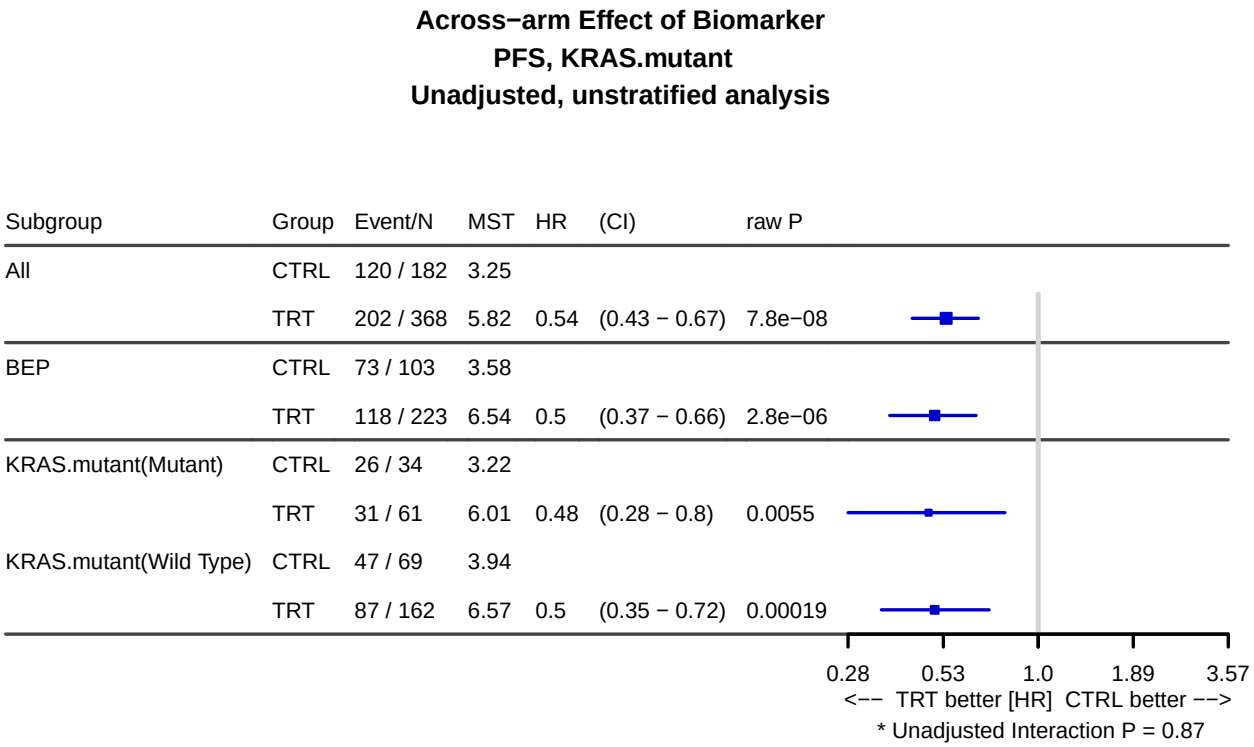
4.1 Estimations within each subgroup

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,"_group")
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)
```

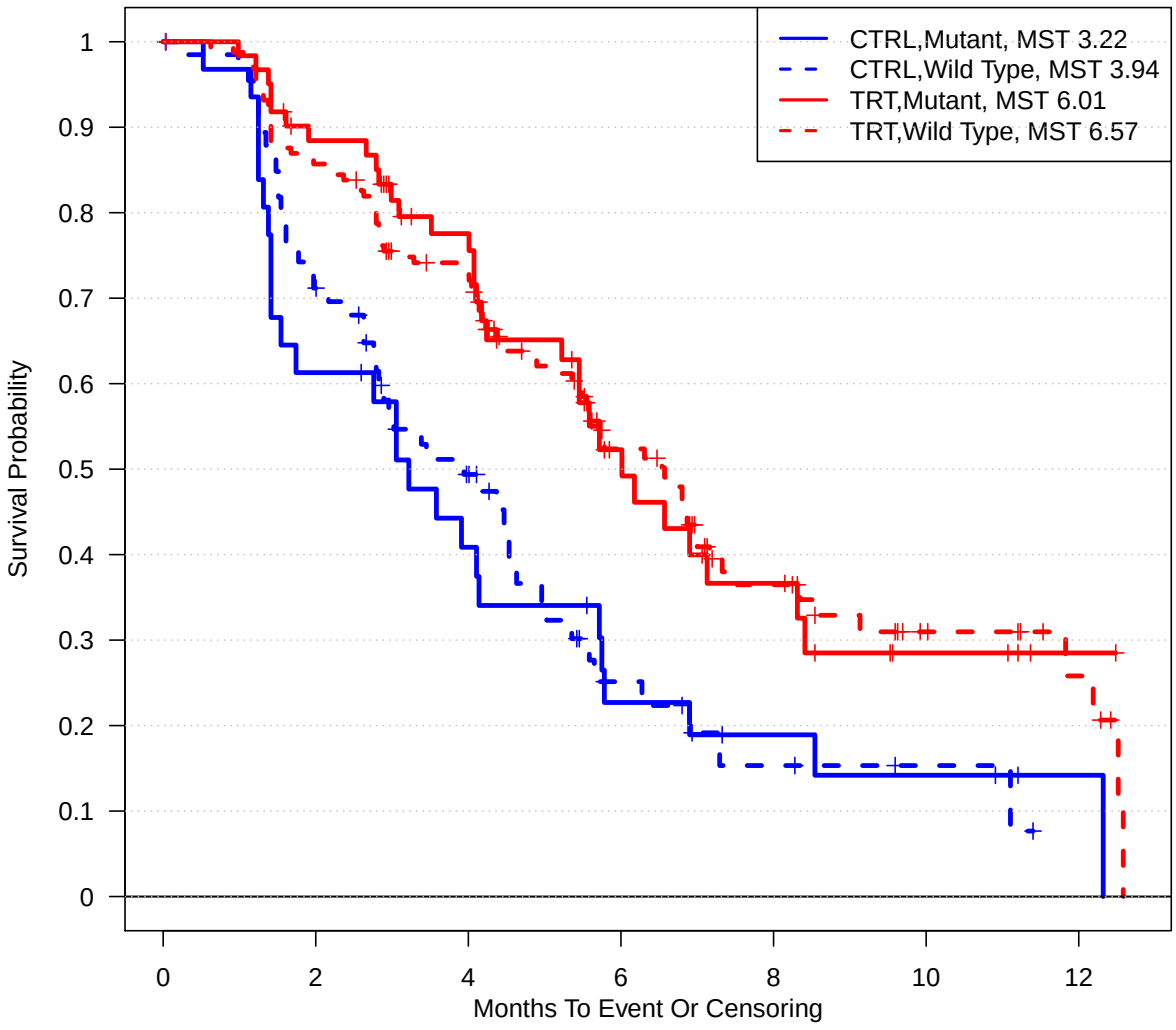
```
## Some patients have missing outcome. Exclude these patients from ITT.
## Some NAs in var column, will define the non NA entries as BEP
```



4.2 KM curves

The following figure show KM curves of the biomarker subgroups:

```
km.out <- PlotKM(data=input, tte=outcome.var[1],cen=outcome.var[2], bep=BEP,
        trt=trt, var=bm2, var.class="categorical",
        legend.loc="topright",
        plot.median=FALSE)
```



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

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.

```
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

	KRAS.mutant_Mutant(CTRL)	KRAS.mutant_Wild Type(CTRL)	KRAS.mutant_Mutant(TRT)	KRAS.mutant_Wild Type(TRT)
Median	52	52	54	53
Min-Max	36...77	32...85	34...89	33...82
NA's	0	0	0	0

The following plot show treatment effect estimations in smaller subgroups defined by both biomarker and clinical variables. For numerical clinical variable, it is dichotomized by its median.

```
res.subgroup.cov <- PlotTabForestMulti(data=input,
                                       outcome.class=outcome.class,
                                       outcome.var=outcome.var,
                                       trt=trt,
                                       var=clinical.vars,
                                       var.class=clinical.vars.class,
                                       compare.bep.itt=FALSE,
                                       compare.subgroup=TRUE,
                                       subgroup=bm2,
                                       covariate=covariate, strata=strata
                       )
```

```
## Some patients have missing outcome. Exclude these patients from ITT.
## Some patients have missing outcome. Exclude these patients from ITT.
## Some patients have missing outcome. Exclude these patients from ITT.
## Some patients have missing outcome. Exclude these patients from ITT.
```

Across arm, Compare KRAS.mutant subgroup

PFS

Unadjusted, unstratified analysis