Biomarker analysis report

2017-08-29

Contents

1 The dataset

The dataset have 368 entries. In which 309 are in biomarker evaluable population (BEP).

- Endpoint of interest: PFS
- Biomarker: KRAS.exprs
- Biomarker type: numeric

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

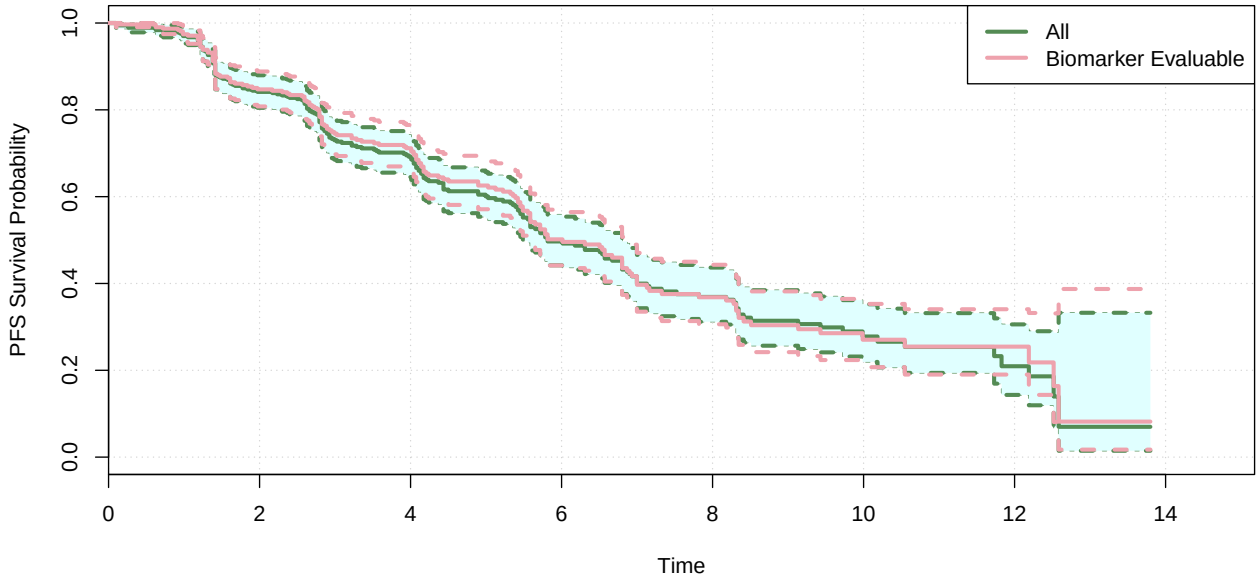
```
kable(SummaryVars(data=input, trt=trt, subgroup=BEP, subgroup.indicator = BEP.indicator, var=clinical.va
```

	All	BEP
Sex		
Total	368	309
NA's	0	0
F	184 (50%)	147 (47.57%)
M	184 (50%)	162 (52.43%)
Age		
N	368	309
Mean	54.03	54.29
Median	54	54
Min-Max	30...89	30...89
NA's	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/null trend of key clinical variables holds in BEP

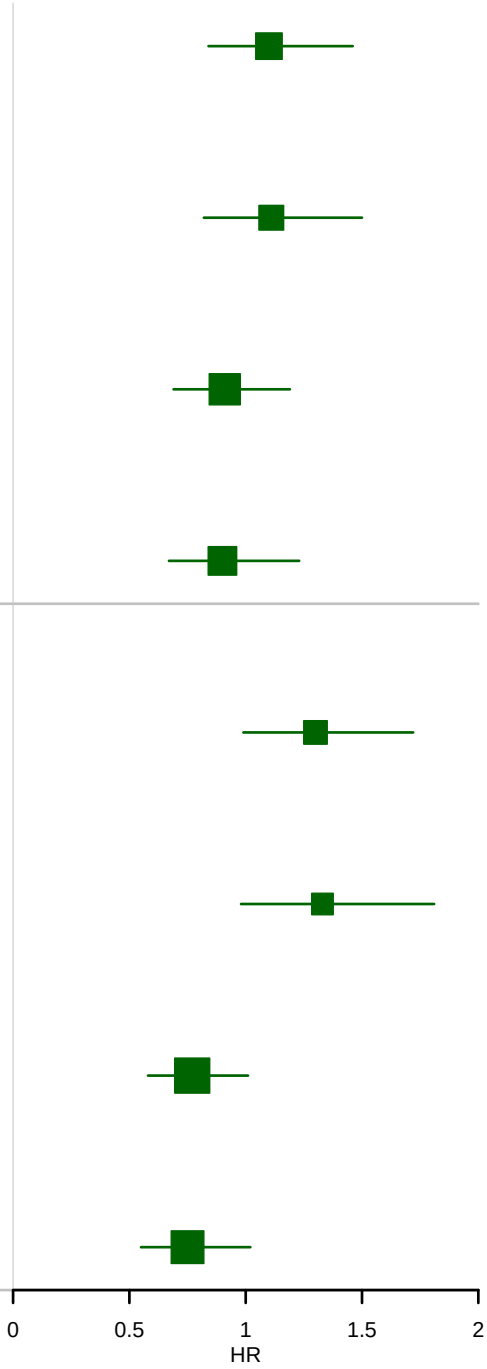
The following forest plot can be used to examine whether any of the key prognostic clinical variables still show prognostic trend in BEP:

```
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.
```

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	85 / 162	6.67			
	Yes	82 / 147	5.72	1.11	(0.82 − 1.5)	0.52
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	82 / 147	5.72			
	Yes	85 / 162	6.67	0.9	(0.67 − 1.23)	0.52
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	73 / 145	6.8			
	Greater	94 / 164	5.59	1.33	(0.98 − 1.81)	0.07
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	94 / 164	5.59			
	Less	73 / 145	6.8	0.75	(0.55 − 1.02)	0.07



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).

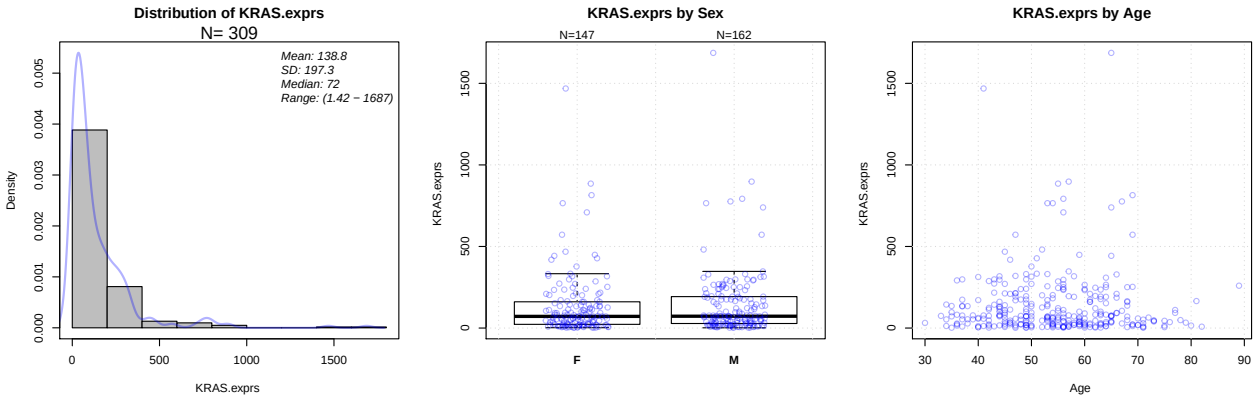
3 Biomarker property and its association to clinical variables

Before performing cutoff exploraotry analysis, it is important to check a biomarker's property. For example, whether this biomarker has a bi-modal or multi modal distribution - if so, this biomarker may has natural cutoff.
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)))
```



4 Biomarker cutoff exploration/selection

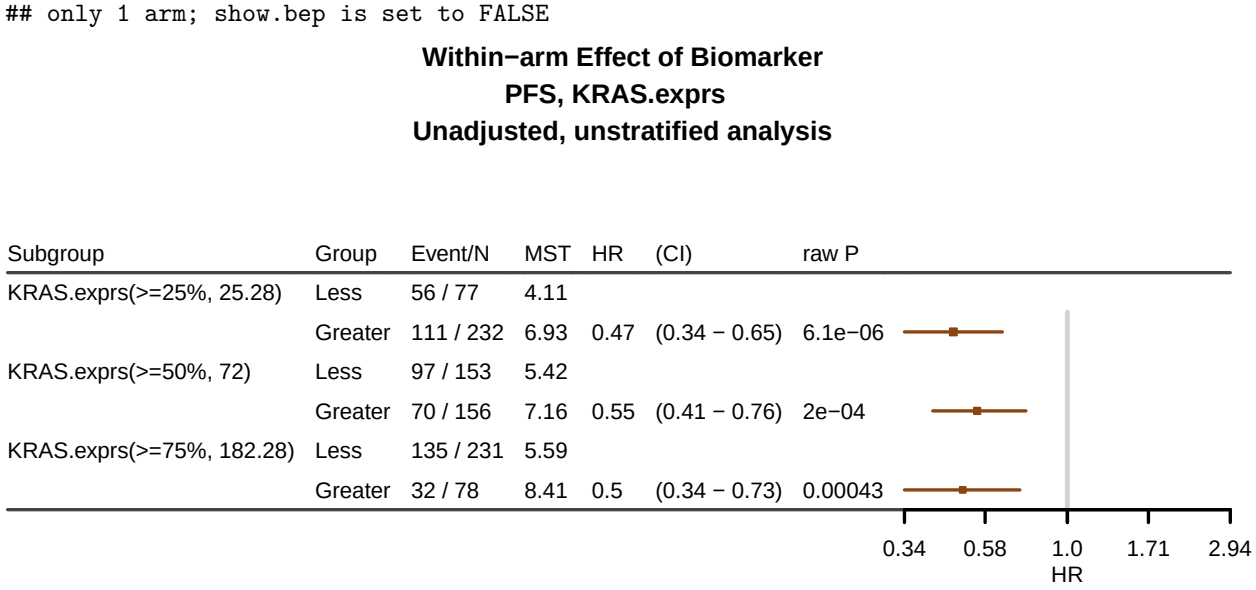
Results in this section could be used to examine multiple candidate cutoffs for a continuous biomarker. The need for cut-off determination should be rooted in the development strategy. In general, an exhaustive search looking at all possible cut-off values is not recommended for decision making. Over-optimized cutoff using one set of clinical data may lead to hard-to-reproduce results. When determining a cutoff, biomarker property should be considered - e.g. cut at a low-dense point may be more robust to population shift. The cutoff selection should also fit the program's stratigitic considerations. There is always a prevalence-effect size trade-off, inputs from multiple functions are needed - for example whether the team is willing to take more risk in PTS (high prevalence, weaker signal) or the team is willing to target at smaller population (lower prevalence, stronger signal)

4.1 Whether the biomarker shows within-arm effect

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

```
res.multicut<- PlotTabForestBiomarker(data=input,
                                      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
```



The forest plots above show within-arm HR of biomarker high (>= cutoff) vs. low (< cutoff) group. 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. For example, within arm, suppose all high vs. low HR are less than 1 and the HR is smaller when cutting at a higher value. This indicates that among patients who received treatment, patients who have higher biomarker value tends to have better clinical outcome .

5 Biomarker subgroup analysis (using selected cutoff)

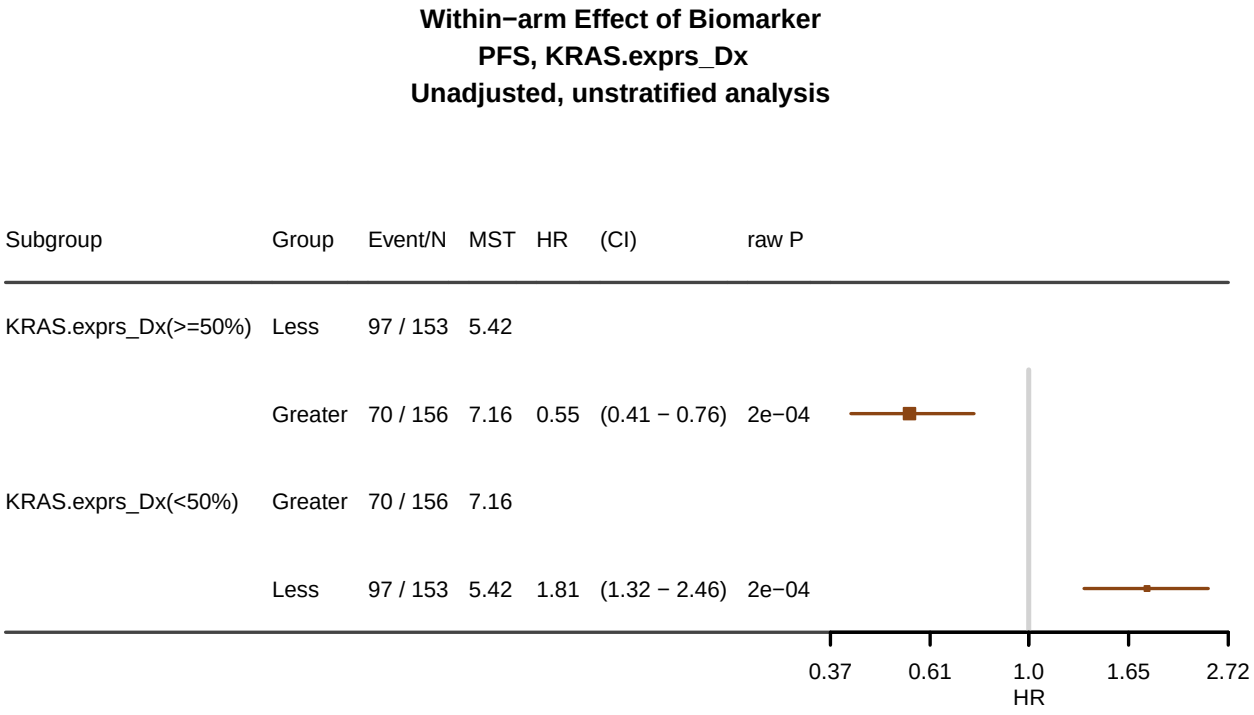
5.1 Estimations within each subgroup

The following figure shows estimate of treatment effect in biomarker subgroups, defined by the selected cutoff.

```
if(bm.class=="numeric"){
if(!is.null(numerical.finalcut)) levs <- paste0(c(">=","<"),numerical.finalcut)
```

```r
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)
```

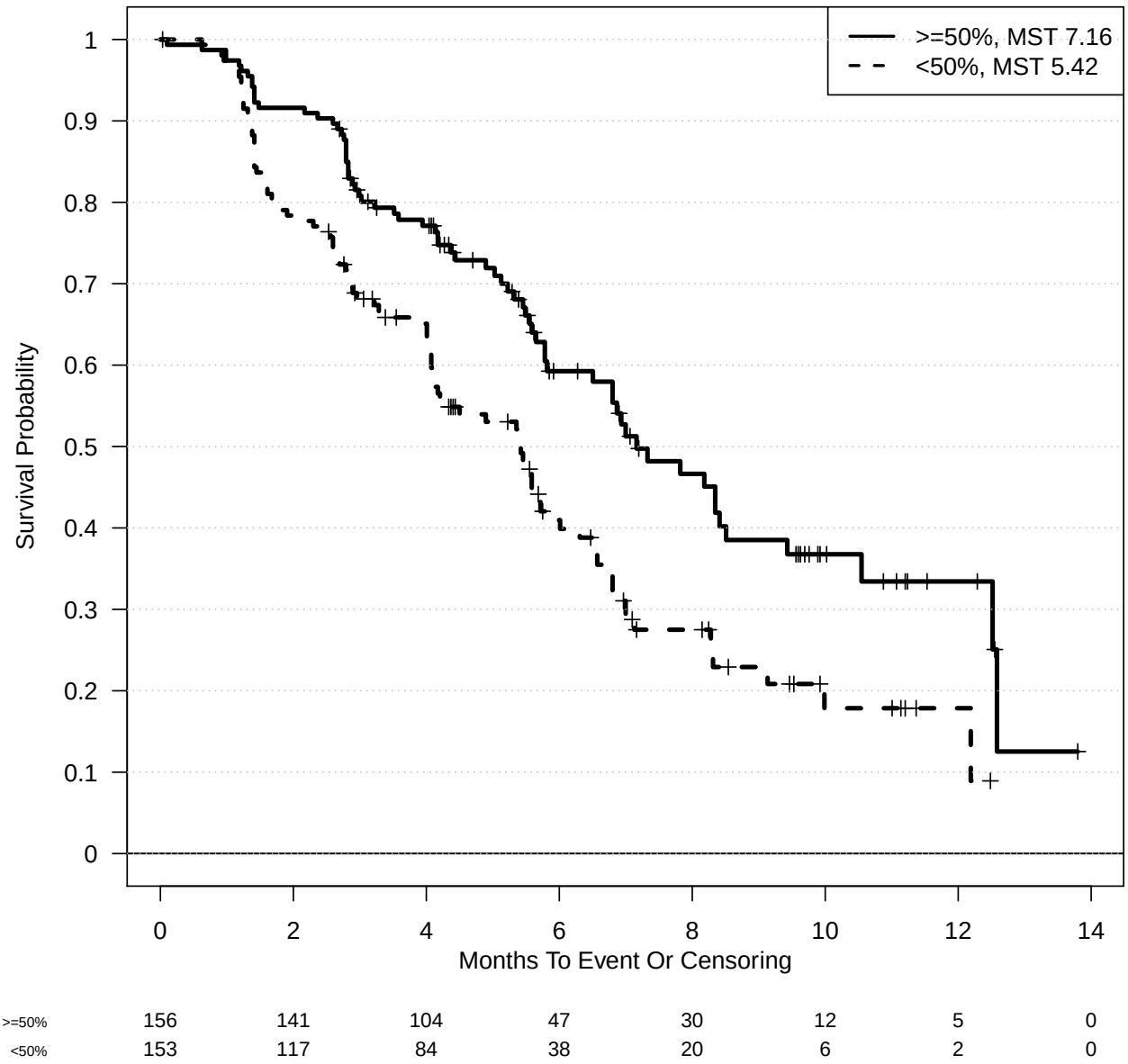
```
## Some patients have missing outcome. Exclude these patients from ITT.

## 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
```



5.2 KM curves

The following figure show KM curves of the biomarker subgroups, based on selected cutoff:

```
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)
```



5.3 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 high and low group.

```
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.exprs_Dx_>=50%	KRAS.exprs_Dx_<50%
Sex		
Total	156	153
NA's	0	0
F	72 (46.15%)	75 (49.02%)
M	84 (53.85%)	78 (50.98%)
Age		
N	156	153
Mean	53.34	55.25
Median	53	55

	KRAS.exprs_Dx_>=50%	KRAS.exprs_Dx_<50%
Min-Max	33. . . 89	30. . . 82
NA's	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.
```

Within arm, Compare KRAS.exprs_Dx subgroup

PFS

Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
>=50% Sex(F)	No	33 / 84	7.33			
	Yes	37 / 72	6.87	1.3	(0.81 − 2.08)	0.28
<50% Sex(F)	No	52 / 78	5.49			
	Yes	45 / 75	5.39	0.98	(0.66 − 1.47)	0.94
>=50% Sex(M)	No	37 / 72	6.87			
	Yes	33 / 84	7.33	0.77	(0.48 − 1.24)	0.28
<50% Sex(M)	No	45 / 75	5.39			
	Yes	52 / 78	5.49	1.02	(0.68 − 1.52)	0.94
>=50% Age(>=50%, 53)	Less	33 / 76	7.33			
	Greater	37 / 80	7	1.03	(0.65 − 1.65)	0.9
<50% Age(>=50%, 55)	Less	45 / 72	5.72			
	Greater	52 / 81	4.17	1.24	(0.83 − 1.85)	0.29
>=50% Age(<50%, 53)	Greater	37 / 80	7			
	Less	33 / 76	7.33	0.97	(0.61 − 1.55)	0.9
<50% Age(<50%, 55)	Greater	52 / 81	4.17			
	Less	45 / 72	5.72	0.81	(0.54 − 1.2)	0.29