Biomarker analysis report

2017-08-29

Contents

1 The dataset

The dataset have 368 entries. In which 223 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

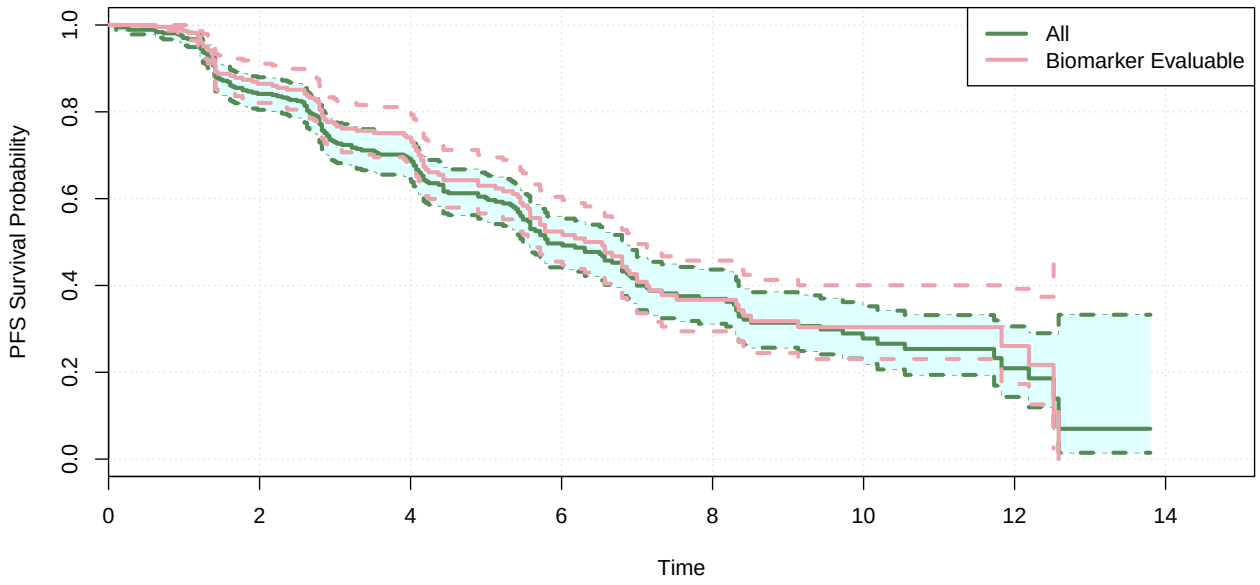
```
kable(SummaryVars(data=input, trt=trt, subgroup=BEP, subgroup.indicator = BEP.indicator, var=clinical.va
```

	All	BEP
Sex		
Total	368	223
NA's	0	0
F	184 (50%)	111 (49.78%)
M	184 (50%)	112 (50.22%)
Age		
N	368	223
Mean	54.03	54.27
Median	54	54
Min-Max	30...89	33...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

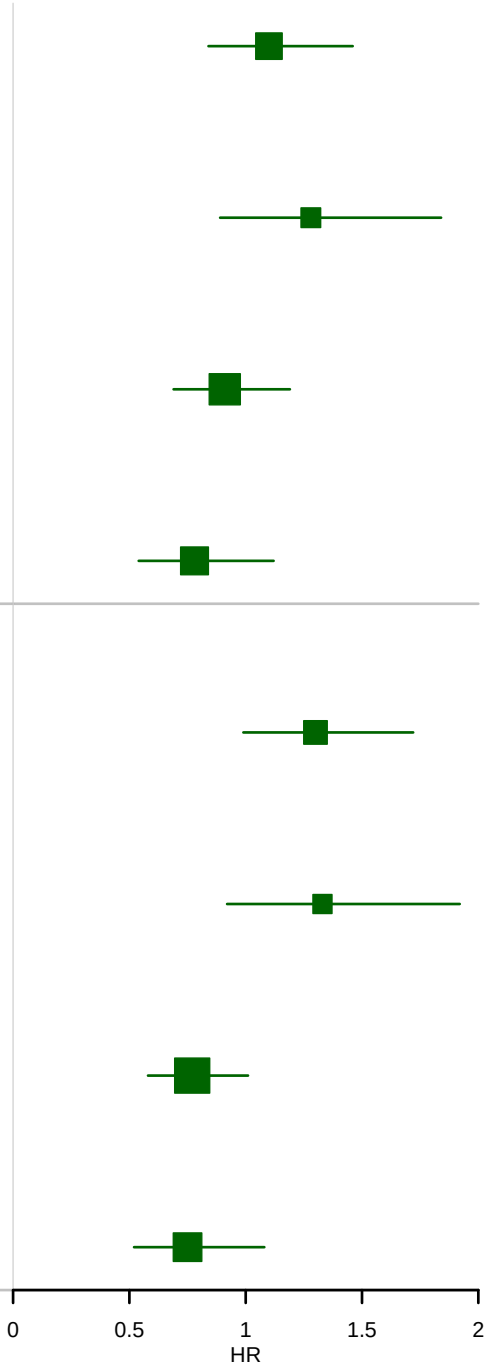
The following forest plot can be used to examine whether any of the key prognostic clinical variables still show prognostic trend in BEP:

```
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	54 / 112	6.8			
	Yes	64 / 111	5.59	1.28	(0.89 − 1.84)	0.18
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	64 / 111	5.59			
	Yes	54 / 112	6.8	0.78	(0.54 − 1.12)	0.18
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	52 / 108	6.8			
	Greater	66 / 115	5.72	1.33	(0.92 − 1.92)	0.13
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	66 / 115	5.72			
	Less	52 / 108	6.8	0.75	(0.52 − 1.08)	0.13



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).

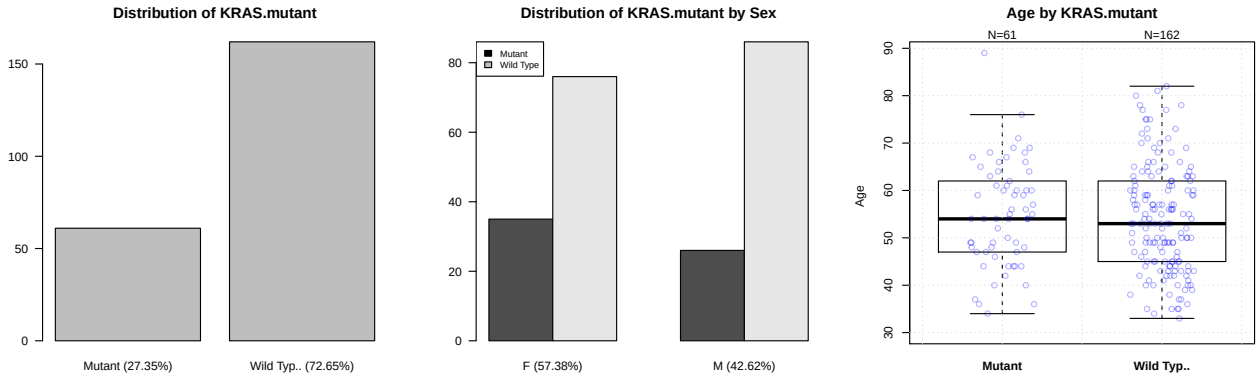
3 Biomarker property and its association to clinical variables

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)))
```



4 Biomarker subgroup analysis

4.1 Estimations within each subgroup

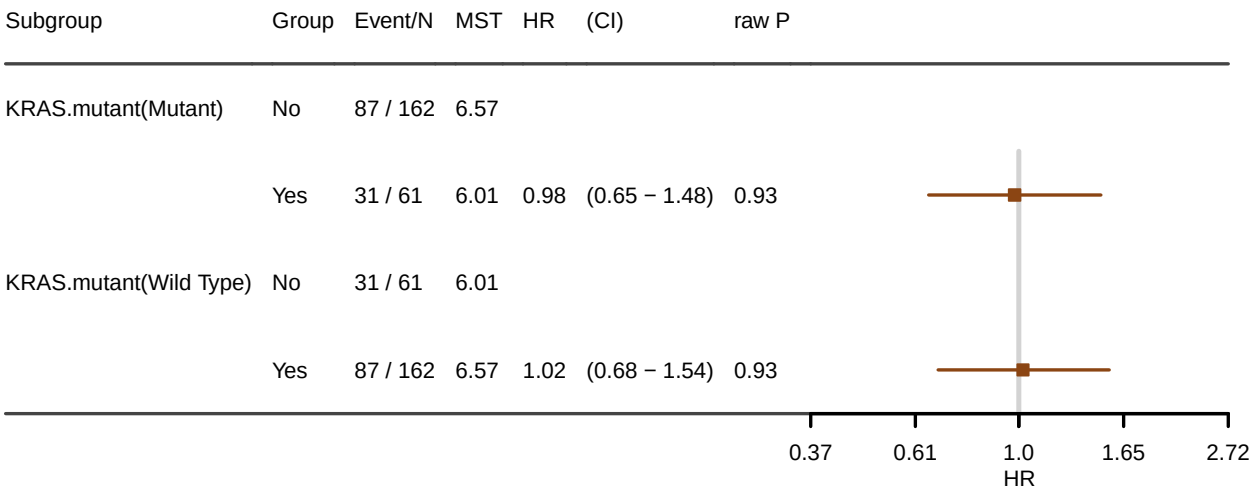
The following figures investigate whether the biomarker shows a within-arm effect (e.g. patients within one biomarker subgroup tend to have better clinical outcome):

```
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
## 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.mutant
Unadjusted, unstratified analysis



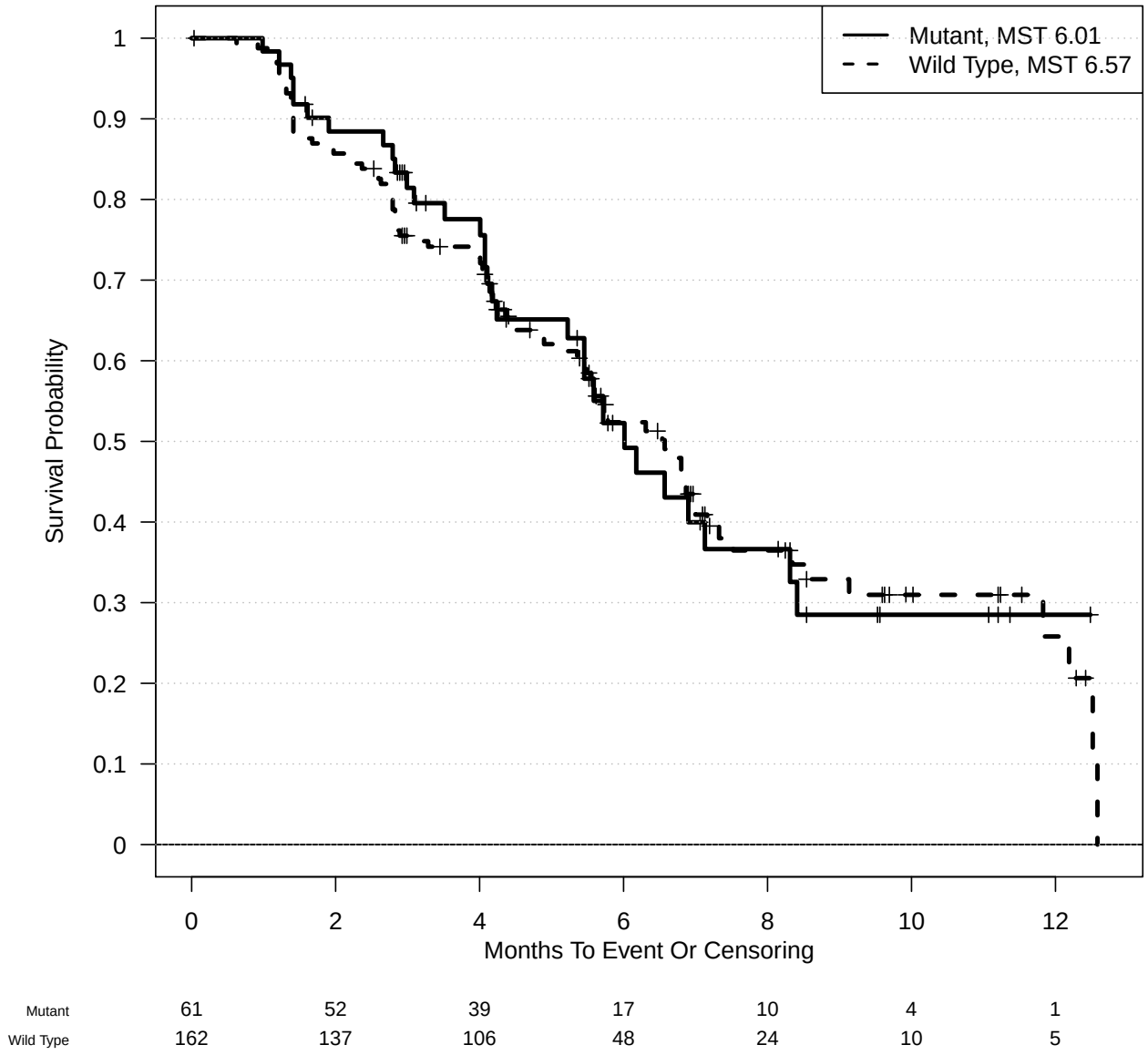
The forest plots above show within-arm HR across biomarker subgroups. For a given arm, if the HR is not all around 1, it indicates that within this arm the biomarker has an association to the clinical outcome.

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)
```



Mutant	61	52	39	17	10	4	1
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	KRAS.mutant_Wild Type
Sex		
Total	61	162
NA's	0	0
F	35 (57.38%)	76 (46.91%)

	KRAS.mutant_Mutant	KRAS.mutant_Wild Type
M	26 (42.62%)	86 (53.09%)
Age		
N	61	162
Mean	54.92	54.03
Median	54	53
Min-Max	34...89	33...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.mutant subgroup

PFS

Unadjusted, unstratified analysis

Subgroup	Group	Event/N	MST	HR	(CI)	raw P
Mutant Sex(F)	No	9 / 26	8.31			
	Yes	22 / 35	5.22	2.44	(1.12 − 5.31)	0.025
Wild Type Sex(F)	No	45 / 86	6.67			
	Yes	42 / 76	6.31	1.04	(0.68 − 1.59)	0.86
Mutant Sex(M)	No	22 / 35	5.22			
	Yes	9 / 26	8.31	0.41	(0.19 − 0.89)	0.025
Wild Type Sex(M)	No	42 / 76	6.31			
	Yes	45 / 86	6.67	0.96	(0.63 − 1.47)	0.86
Mutant Age(>=50%, 54)	Less	12 / 25	7.13			
	Greater	19 / 36	6.01	1.23	(0.59 − 2.53)	0.58
Wild Type Age(>=50%, 53)	Less	35 / 75	6.8			
	Greater	52 / 87	5.72	1.27	(0.83 − 1.96)	0.28
Mutant Age(<50%, 54)	Greater	19 / 36	6.01			
	Less	12 / 25	7.13	0.82	(0.39 − 1.69)	0.58
Wild Type Age(<50%, 53)	Greater	52 / 87	5.72			
	Less	35 / 75	6.8	0.79	(0.51 − 1.21)	0.28