FULL LCA Analysis

P R Barber 22 October 2019

load(file = "COIN_Final.Rdata")

Forest plot of covariates

Loading required package: stringr

Covariate	Class	Hazard Ratio (95% CI)	p-value
TRT arm B	1 -+:	0.71 (0.45– 1.14)	0.16
WHO performance status	1	─→ 3.08 (1.79– 5.28)	<0.001***
Adj. Chemo >1m <6m ago	1	1.01 (0.67– 1.51)	0.96
Sum of longest diameter	1	─← 4.34 (2.80− 6.72)	<0.001***
Number of mets sites	1 +	— 1.45 (0.92– 2.29)	0.11
EREG Cq value (negated)	1 —	0.42 (0.23– 0.74)	0.003**
RAS mutation	1	── 3.81 (2.06– 7.04)	<0.001***
BRAF mutation	1 -+:	0.84 (0.51– 1.38)	0.49
Neutrophil count	1	1.32 (1.00– 1.73)	0.05*
Alkaline phosphatase	1 :+-	1.23 (0.89– 1.69)	0.22
Pain	1 —	1.78 (1.06– 2.97)	0.03*
TRT arm B	2 -	0.94 (0.70– 1.25)	0.66
WHO performance status	2	0.88 (0.63– 1.21)	0.42
Adj. Chemo >1m <6m ago	2 -	← 1.93 (1.46– 2.56)	<0.001***
Sum of longest diameter	2 →	— 1.60 (1.20 – 2.13)	0.001**
Number of mets sites	2 -	← 1.91 (1.44– 2.54)	<0.001***
EREG Cq value (negated)	2 —————————————————————————————————————	0.94 (0.67– 1.31)	0.71
RAS mutation	2	- 1.25 (0.87– 1.79)	0.22
BRAF mutation	2	─← 3.47 (2.32– 5.17)	<0.001***
Neutrophil count	2 -	1.06 (0.85– 1.32)	0.62
Alkaline phosphatase	2	─→ 6.87 (3.88–12.18)	<0.001***
Pain	2	- 1.40 (1.04– 1.90)	0.03*
TRT arm B	3	1.38 (1.10– 1.72)	0.005**
WHO performance status	3 →	1.30 (1.01– 1.66)	0.04*
Adj. Chemo >1m <6m ago	3 -	1.24 (0.99– 1.54)	0.06
Sum of longest diameter	3 -	0.93 (0.73– 1.18)	0.55
Number of mets sites	3	1.01 (0.81– 1.26)	0.94
EREG Cq value (negated)	3 →	0.67 (0.51– 0.88)	0.004**
RAS mutation	3 –	← 1.86 (1.41– 2.46)	<0.001***
BRAF mutation	3 -	- 1.46 (1.16– 1.83)	0.001**
Neutrophil count	3	→ 2.91 (2.25– 3.77)	<0.001***
Alkaline phosphatase	3 →	0.87 (0.72– 1.06)	0.16
Pain	3 -	← 1.89 (1.52– 2.36)	<0.001***
	<u> </u>		
	0.2 0.5 1	2 5 10	
	HR		

KM Curves

```
library(survival)

data <- patient_data

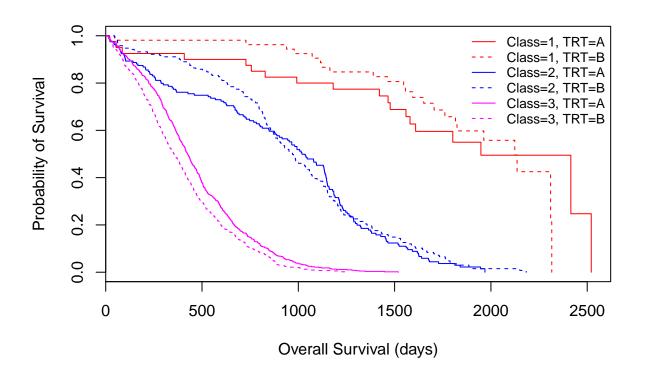
data$SurvObj.os <- with(data, Surv(ostime, osevent))
data$SurvObj.pfs <- with(data, Surv(pfstime, pfsevent))

col=c("red", "red", "blue", "blue", "magenta", "magenta")
lty=c(1,2,1,2,1,2)</pre>
```

OS

```
# rename
data$Class <- data$Class.OS

km <- survfit(SurvObj.os ~ Class + TRT, data=data)
plot(km, col=col, lty=lty, xlab="Overall Survival (days)", ylab="Probability of Survival")
legend("topright", col=col, legend = names(km$strata), lty=lty, bty="n", cex=0.8)</pre>
```



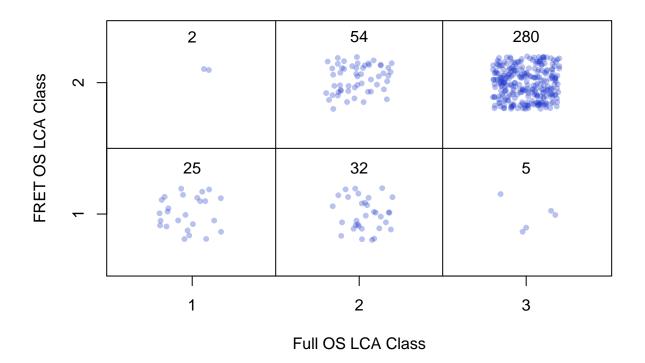
```
print(km)
## Call: survfit(formula = SurvObj.os ~ Class + TRT, data = data)
##
##
                    n events median 0.95LCL 0.95UCL
## Class=1, TRT=A
                           19
                                1948
                                        1580
                                                  NA
                   40
## Class=1, TRT=B 53
                           23
                                2124
                                        1816
                                                  NA
```

```
## Class=2, TRT=A 159
                         150
                                1019
                                         902
                                                1140
## Class=2, TRT=B 191
                                 970
                                         892
                                                1058
                         183
## Class=3, TRT=A 616
                         608
                                 425
                                         402
                                                 448
## Class=3, TRT=B 571
                         560
                                 355
                                         327
                                                 386
survdiff(SurvObj.os ~ Class, data=data)
## Call:
## survdiff(formula = SurvObj.os ~ Class, data = data)
##
              N Observed Expected (0-E)^2/E (0-E)^2/V
## Class=1
             93
                      42
                               258
                                       180.9
## Class=2 350
                     333
                               558
                                        90.6
                                                   153
## Class=3 1187
                                       267.2
                    1168
                               727
                                                   653
##
## Chisq= 728 on 2 degrees of freedom, p= <2e-16
survdiff(SurvObj.os[Class==1] ~ TRT[Class==1], data=data)
## Call:
## survdiff(formula = SurvObj.os[Class == 1] ~ TRT[Class == 1],
##
       data = data)
##
##
                      N Observed Expected (O-E)^2/E (O-E)^2/V
## TRT[Class == 1]=A 40
                               19
                                      18.2
                                              0.0325
                                                         0.0621
## TRT[Class == 1]=B 53
                               23
                                      23.8
                                              0.0250
                                                         0.0621
## Chisq= 0.1 on 1 degrees of freedom, p= 0.8
survdiff(SurvObj.os[Class==2] ~ TRT[Class==2], data=data)
## Call:
## survdiff(formula = SurvObj.os[Class == 2] ~ TRT[Class == 2],
##
       data = data)
##
##
                       N Observed Expected (0-E)^2/E (0-E)^2/V
## TRT[Class == 2]=A 159
                               150
                                        146
                                                0.134
                                                          0.241
## TRT[Class == 2]=B 191
                               183
                                        187
                                                0.104
                                                          0.241
## Chisq= 0.2 on 1 degrees of freedom, p= 0.6
survdiff(SurvObj.os[Class==3] ~ TRT[Class==3], data=data)
## Call:
## survdiff(formula = SurvObj.os[Class == 3] ~ TRT[Class == 3],
##
       data = data)
##
                       N Observed Expected (0-E)^2/E (0-E)^2/V
##
## TRT[Class == 3]=A 616
                               608
                                        676
                                                 6.75
                                                            16.2
## TRT[Class == 3]=B 571
                               560
                                        492
                                                 9.25
                                                            16.2
##
## Chisq= 16.2 on 1 degrees of freedom, p= 6e-05
```

<pre>ggrisktable(km, data=data) + theme_cleantable()</pre>									
1	Number at	risk							
Class=1, TRT=A	40	36	32	24	6	1			
Class=1, TRT=B	53	52	49	38	13	0			
Class=2, TRT=A	159	119	79	18	0	0			
Class=2, TRT=B	191	163	87	27	2	0			
Class=3, TRT=A	616	231	23	1	0	0			
Class=3, TRT=B	571	166	11	0	0	0			

Compare Classes of FRET and FULL LCA

```
as.numeric.factor <- function(x) {as.numeric(levels(x))[x]}
data <- patient_data[patient_data$FRET.cohort==1,]
data$Class.FRET.OS <- as.numeric.factor(data$Class.FRET.OS)
data$Class.OS <- as.numeric.factor(data$Class.OS)</pre>
```



Cohen's Kappa

```
library(irr)
```

```
## Warning: package 'irr' was built under R version 3.5.3
```

^{##} Loading required package: lpSolve

^{##} Warning: package 'lpSolve' was built under R version 3.5.3

kappa2(data[,c("Class.FRET.OS", "Class.OS")])

```
## Cohen's Kappa for 2 Raters (Weights: unweighted)
##
## Subjects = 398
## Raters = 2
## Kappa = 0.00682
##

z = 0.592
## p-value = 0.554
```

Calculate the means and standard deviations from 100,000 random group assignments with the same number per subclass as the real data. Also do permutations test and see how many random group are as, or more, extreme as the real data.

Session Information

sessionInfo()

```
## R version 3.5.1 (2018-07-02)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 16299)
## Matrix products: default
##
## locale:
## [1] LC_COLLATE=English_United Kingdom.1252
## [2] LC_CTYPE=English_United Kingdom.1252
## [3] LC_MONETARY=English_United Kingdom.1252
## [4] LC_NUMERIC=C
##
  [5] LC_TIME=English_United Kingdom.1252
##
## attached base packages:
## [1] stats
                 graphics grDevices utils
                                                datasets methods
                                                                    base
##
## other attached packages:
## [1] irr_0.84.1
                          lpSolve_5.6.13.3
                                              survival_2.42-3
                                              survminer_0.4.6
## [4] filesstrings_3.0.0 stringr_1.3.1
## [7] ggpubr_0.2
                          magrittr_1.5
                                              ggplot2_3.1.1
##
## loaded via a namespace (and not attached):
## [1] zoo_1.8-4
                           tidyselect_0.2.5
                                               purrr_0.2.5
## [4] splines_3.5.1
                           lattice_0.20-35
                                               colorspace_1.3-2
  [7] generics_0.0.2
                           vctrs_0.2.0
                                               htmltools_0.3.6
## [10] yaml_2.2.0
                           survMisc_0.5.5
                                               rlang_0.4.0
## [13] pillar_1.4.1
                           glue_1.3.0
                                               withr_2.1.2
## [16] matrixStats_0.54.0 lifecycle_0.1.0
                                               plyr_1.8.4
## [19] munsell_0.5.0
                           gtable_0.2.0
                                               evaluate_0.12
## [22] labeling_0.3
                           knitr_1.20
                                               broom_0.5.2
## [25] Rcpp_1.0.1
                           xtable_1.8-4
                                               scales_1.0.0
## [28] backports_1.1.2
                           checkmate_1.9.3
                                               km.ci_0.5-2
                           digest_0.6.18
## [31] gridExtra 2.3
                                               stringi 1.2.4
## [34] dplyr_0.8.3
                           KMsurv_0.1-5
                                               grid_3.5.1
```

##	[37]	rprojroot_1.3-2	tools_3.5.1	lazyeval_0.2.1
##	[40]	tibble_2.1.1	crayon_1.3.4	tidyr_1.0.0
##	[43]	pkgconfig_2.0.2	zeallot_0.1.0	Matrix_1.2-14
##	[46]	data.table_1.12.2	strex_1.0.1	assertthat_0.2.0
##	[49]	rmarkdown_1.10	R6_2.3.0	nlme_3.1-137
##	[52]	compiler_3.5.1		