Agentic AI for Adaptive Pharmacogenomic Biomarker Discovery in Cancer

Step 1: Load ICB data (CSV)

```
# load in csv file
filepath <- list.files(here("./data/rawdata"), pattern = "\\.csv$", full.names = TRUE)
dat_icb <- read.csv(filepath, check.names = FALSE)

# define which columns are expression features clinical/metadata
# first 10 columns are clinical/metadata
genes <- colnames(dat_icb)[-c(1:10)]

# perform basic checks
stopifnot(all(c("survival_time_os", "event_occurred_os") %in% colnames(dat_icb)))
stopifnot(is.numeric(dat_icb$survival_time_os))
stopifnot(all(dat_icb$event_occurred_os %in% c(0, 1, NA)))
```

Step 2: Compute C-index using continuous markers (recommended)

C-index here assesses how well a marker ranks patients by risk. For expression, use the continuous values for best use of information.

```
ci_cont <- lapply(1:length(genes), function(k){

# concordance index
ci <- concordance.index(
  x = dat_icb[, genes[k]],
  surv.time = dat_icb$survival_time_os,
  surv.event = dat_icb$event_occurred_os,
  method = "noether"
)

data.frame(
  gene = genes[k],
  c.idex = ci$c.index,
  ci.lower = ci$lower,
  ci.upper = ci$upper,
  pval = ci$p.value,
  cancer_type = unique(dat_icb$cancer_type),
  treatment = unique(dat_icb$treatment))
})

ci_cont <- do.call(rbind, ci_cont)
head(ci_cont)
```

```
##      gene    c.idex  ci.lower  ci.upper        pval cancer_type  treatment
```

```
## 1   ITGAL 0.3464448 0.2183384 0.4745511 0.018807770    Melanoma PD-1/PD-L1
## 2   RGPD5 0.4478064 0.3077270 0.5878857 0.465216732    Melanoma PD-1/PD-L1
## 3 HERPUD1 0.3540091 0.2433087 0.4647095 0.009743928    Melanoma PD-1/PD-L1
## 4   USP36 0.4372163 0.3104883 0.5639444 0.331545256    Melanoma PD-1/PD-L1
## 5  SLC2A3 0.4311649 0.3028393 0.5594905 0.293100800    Melanoma PD-1/PD-L1
## 6   DDX3Y 0.5000000 0.3724432 0.6275568 1.000000000    Melanoma PD-1/PD-L1
```

```
write.csv(ci_cont, file = here("./data/results/ci_cont.csv"))
```

Step 3: Compute C-index using binary markers (High vs Low, median split)

This is mainly useful for demonstration/visualization (KM curves), but it discards information compared with continuous markers.

```
ci_bin <- lapply(1:length(genes), function(k){

cut <- median( dat_icb[, genes[k]], na.rm = TRUE)
g <- as.integer( dat_icb[, genes[k]] >= cut)  # High=1, Low=0

ci <- concordance.index(x = g,
                        surv.time = dat_icb$survival_time_os,
                        surv.event = dat_icb$event_occurred_os,
                        method="noether")


data.frame(gene = genes[k],
           c.idex = ci$c.index,
           ci.lower = ci$lower,
           ci.upper = ci$upper,
           pval = ci$p.value,
           cancer_type = unique(dat_icb$cancer_type),
           treatment = unique(dat_icb$treatment))


})

ci_bin <- do.call(rbind, ci_bin)
head(ci_bin)
```

```
##      gene    c.idex  ci.lower  ci.upper       pval cancer_type  treatment
## 1   ITGAL 0.3314286 0.1452747 0.5175825 0.07592380    Melanoma PD-1/PD-L1
## 2   RGPD5 0.5178571 0.3182441 0.7174702 0.86081559    Melanoma PD-1/PD-L1
## 3 HERPUD1 0.2910663 0.1185903 0.4635422 0.01758423    Melanoma PD-1/PD-L1
## 4   USP36 0.4434524 0.2438137 0.6430911 0.57878566    Melanoma PD-1/PD-L1
## 5  SLC2A3 0.3768546 0.1882731 0.5654361 0.20058952    Melanoma PD-1/PD-L1
## 6   DDX3Y 0.5769231 0.3766904 0.7771558 0.45147617    Melanoma PD-1/PD-L1
```

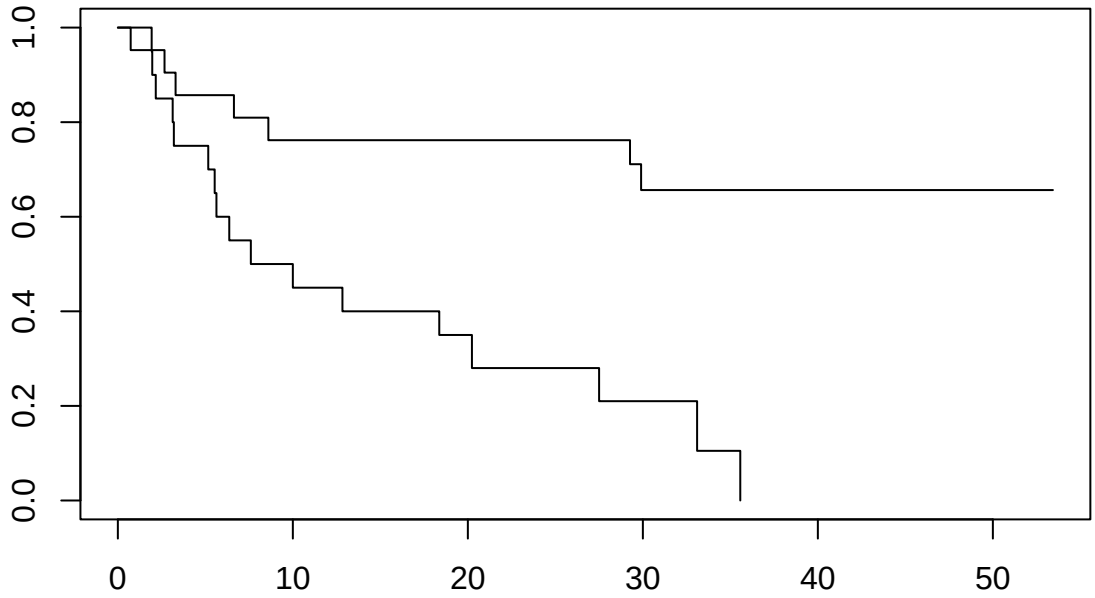
```
write.csv(ci_bin, file = here("./data/results/ci_bin.csv"))
```

Notes / next steps

- Known ICB-related markers often discussed include: LAG3, TIGIT, CD274 (PD-L1).

- If you want a simple KM plot for one marker:

```
cut <- median(dat_icb$LAG3, na.rm=TRUE)
dat_icb$LAG3_group <- ifelse(dat_icb$LAG3 >= cut, "High", "Low")
fit <- survfit(Surv(survival_time_os, event_occurred_os) ~ LAG3_group, data=dat_icb)
plot(fit)
```



- If you want to use an ORCESTRA-derived MultiAssayExperiment (MAE) instead of CSV: you can load the MAE, extract a SummarizedExperiment, then build a clean data.frame with survival + markers for the same workflow above.

```
library(PredictioR)

files <- list.files(file.path(dir_input, 'rds'))
dat <- readRDS(file.path(dir_input, 'rds', files))
dat_icb <- createSE(dat)
expr <- assay(dat_icb)
clin <- colData(expr)

# From here, you'd create dat_icb-like object:
dat_icb <- data.frame(
  survival_time_os  = clin$survival_time_os,
  event_occurred_os = clin$event_occurred_os,
  t(expr[c("LAG3","CD274"), ]) |> t()  # or compute signature scores first
)
```