

Supplementary Table 1. Patient Characteristics

All cancers		514
	Median age in years (range)	60.8 (23.9–93.3)
	Male	204 (39.7%)
	Female	310 (60.3%)
Tumor histology**		
	Breast Cancer	49 (9.53%)
	Colorectal Cancer	140 (27.24%)
	Esophageal Cancer	17 (3.31%)
	Head and Neck Cancer	12 (2.33%)
	Liver and Bile Duct Cancer	19 (3.70%)
	Lung Cancer	20 (3.89%)
	Melanoma	6 (1.17%)
	Neuroendocrine Tumors	15 (2.92%)
	Ovarian Cancer	43 (8.37%)
	Pancreatic Cancer	55 (10.70%)
	Sarcoma	24 (4.67%)
	Small Intestine Cancer	12 (2.33%)
	Stomach Cancer	25 (4.86%)
	Unknown Primary Cancer	13 (2.53%)
	Uterine Cancer	24 (4.67%)
	All other*	40 (7.78%)
	Total	514

*Other cancers: Adrenal Cortical Carcinoma = 3; Basal Cell Carcinoma of the Skin = 1; Bladder Cancer = 4; Brain and Nervous System Cancer = 3; Cervical Cancer = 5; Gallbladder and Extrahepatic Bile Duct Cancer = 4; Kidney and Renal Pelvis Cancer = 3; Lipomatous Neoplasm = 2; Mesothelioma = 2; Ocular Melanoma = 1; Primary Peritoneal Carcinoma = 1; Prostate Cancer = 4; Squamous Cell Carcinoma of the Skin = 3; Thymic Cancer = 1; Thyroid Cancer = 3

**Pathologic classification provided here represents the most recent review; also, ocular melanoma was not included under melanoma

Supplementary Table 2: types of immunotherapy received in 217 patients

	Number of patients
All patients treated with immune checkpoint blockade	217
Anti-PD-1/PD-L1-based therapy	215
Anti-CTLA-4 therapy	2
Combination anti-PD-1/PDL-1 and anti-CTLA-4 therapy	16

Supplementary Table 3. Immune checkpoint proteins and their function

Molecule	Full name	Function	References
BTLA (CD272)	B and T cell lymphocyte attenuator	Binds to TNFRSF14 ligand on T cell lymphocytes leading to decreased cell activation and proliferation	Wojciechowicz et al 2022 [23]
CTLA-4 (CD152)	Cytotoxic T-lymphocyte antigen 4	Inhibits T cell activation by antagonizing CD28-mediated co-stimulation of T cells	Rowshanravan et al 2018 [24]
LAG-3 (CD223)	Lymphocyte Activation Gene-3	Binds to MHCII and inhibits T cell activation by interfering with the association of CD4 with MHCII	Maruhashi et al 2020 [25]
NECTIN2 (CD112)	Nectin Cell Adhesion Molecule 2 Poliovirus Receptor-Related-2	Binds to T cell immunoglobulin and ITIM domain (TIGIT) to serve as a co-inhibitory signal for human T cells as well as NK and NKT cells	Stamm et al 2018 [26], Zhu et al 2016 [27]
PVR (CD155, TIGIT ligand)	Poliovirus Receptor	Binds to TIGIT to diminish T cell and NK cell activity	Stanietsky et al 2009 [28]
TIGIT	T-Cell Immunoglobulin and ITIM Domain	Interacts with PVR and its related proteins to inhibit both T cell activity and NK cytotoxicity	Stanietsky et al 2009 [28]
TIM-3	T-Cell Immunoglobulin- and Mucin-Domain-Containing Molecule-3	Inhibits Th1 responses and cytokine secretion and is correlated with T-cell exhaustion	Wolf et al 2020 [29]
TNFRSF14 (BTLA ligand)	Herpesvirus entry mediator	Acts as a ligand for BTLA to inhibit T lymphocyte proliferation	Steinberg et al 2011 [30]
VISTA	V-Domain Immunoglobulin Suppressor of T-Cell Activation	Inhibits T-cell proliferation, cytokine release by binding to V-set and immunoglobulin domain containing 3 (VSIG3) Binds to Galectin-9 to induce T cell apoptosis	Xu et al 2019 [31]

Supplementary Data 1: De-identified data

Please refer to separate excel file titled "Supplementary Data 1".

Supplementary Data 2: Analytic Code

```
read_excel("Supplemental_Table_individual_npjgm_030724.xlsx", sheet = 1) -> roo
roo %>% names()
```

```
## [1] "ID" "Age" "Gender"
## [4] "Diagnosis" "TMB10" "TMB20"
## [7] "PD-L1 IHC positivity" "MSI-H" "BTLA"
## [10] "CTLA4" "LAG3" "NECTIN2"
## [13] "PD-1" "PD-L1" "PD-L2"
## [16] "PVR" "TIGIT" "TIM3"
## [19] "TNFRSF14" "VISTA" "IO"
## [22] "OS from Dx date" "OS event" "OS from IO date"
## [25] "PFS from IO date" "PFS event" "Administered_agent"
```

```
roo %>% mutate(PD1_high=case_when(
  .$`PD-1` >= 75 ~ 1,
  .$`PD-1` < 75 ~ 0
)) -> roo
(roo$PD1_high %>% table())
```

```
## .
## 0 1
## 421 93
```

```
(roo$PD1_high %>% table()) / nrow(roo)
```

```
## .
## 0 1
## 0.8190661 0.1809339
```

```
roo$PD1_high_c <- ifelse(roo$PD1_high==1,"High","Low")
```

- A total of 93 patients (18.1%) showed high expression of PD-1.

```
roo$lung <- ifelse(roo$Diagnosis=="Lung Cancer", 1, 0)
roo$colon <- ifelse(roo$Diagnosis=="Colorectal Cancer", 1, 0)
roo$breast <- ifelse(roo$Diagnosis=="Breast Cancer", 1, 0)
roo$ovarian <- ifelse(roo$Diagnosis=="Ovarian Cancer", 1, 0)
roo$panc <- ifelse(roo$Diagnosis=="Pancreatic Cancer", 1, 0)
roo$uterine <- ifelse(roo$Diagnosis=="Uterine Cancer", 1, 0)
roo$net <- ifelse(roo$Diagnosis=="Neuroendocrine Tumors", 1, 0)
roo$sarcoma <- ifelse(roo$Diagnosis=="Sarcoma", 1, 0)
roo$melanoma <- ifelse(roo$Diagnosis=="Melanoma",1, 0)
```

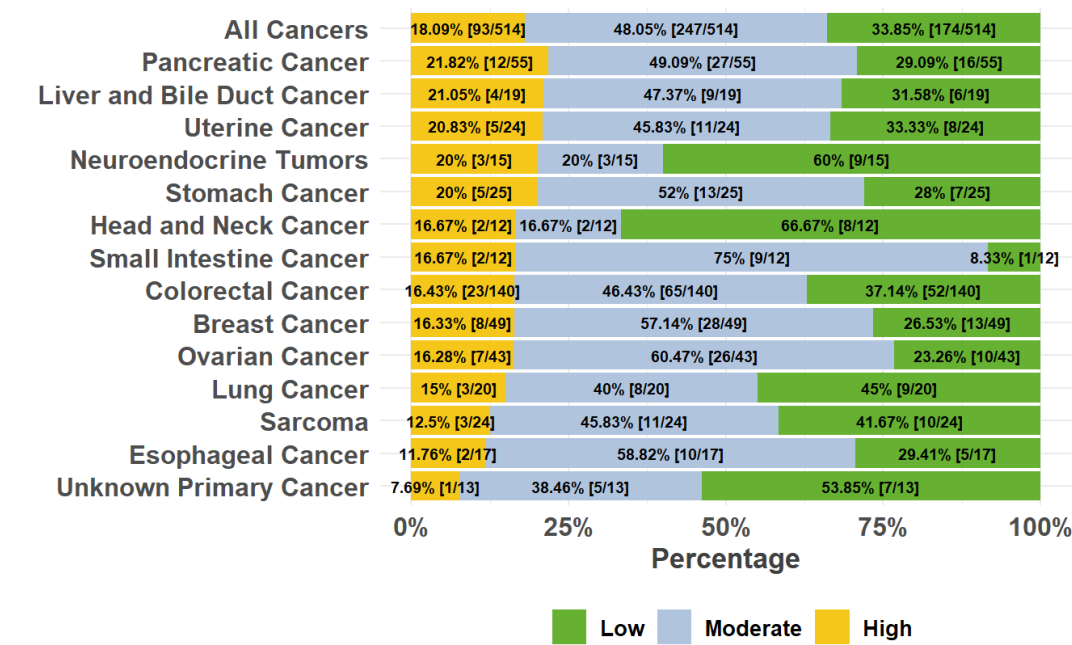
Table 1 (Supplemental)

```
roo %>% select(Age, Gender, Diagnosis) %>%
gtsummary::tbl_summary(
  statistic = list(all_continuous() ~ "{median} ({min}, {max})")
)
```

Characteristic	N = 514 [†]
Age	61 (24, 93)
Gender	
Female	310 (60%)
[†] Median (Range); n (%)	

Characteristic	N = 514 [†]
Male	204 (40%)
Diagnosis	
adrenal cortical carcinoma	1 (0.2%)
Adrenal Gland Cancer	2 (0.4%)
Basal Cell Carcinoma of the Skin	1 (0.2%)
Bladder Cancer	4 (0.8%)
Brain and Nervous System Cancer	3 (0.6%)
Breast Cancer	49 (9.5%)
Cervical Cancer	5 (1.0%)
Colorectal Cancer	140 (27%)
Esophageal Cancer	17 (3.3%)
Gallbladder and Extrahepatic Bile Duct Cancers	4 (0.8%)
Head and Neck Cancer	12 (2.3%)
Kidney and Renal Pelvis Cancer	3 (0.6%)
Lipomatous Neoplasms	2 (0.4%)
Liver and Bile Duct Cancer	19 (3.7%)
Lung Cancer	20 (3.9%)
Melanoma	6 (1.2%)
Mesothelioma	2 (0.4%)
Neuroendocrine Tumors	15 (2.9%)
ocular melanoma	1 (0.2%)
Ovarian Cancer	43 (8.4%)
Pancreatic Cancer	55 (11%)
primary peritoneal carcinoma	1 (0.2%)
Prostate Cancer	4 (0.8%)
Sarcoma	24 (4.7%)
Small Intestine Cancer	12 (2.3%)
Squamous Cell Carcinoma of the Skin	3 (0.6%)
Stomach Cancer	25 (4.9%)
Thymic Cancer	1 (0.2%)
Thyroid Cancer	3 (0.6%)
Unknown Primary Cancer	13 (2.5%)
Uterine Cancer	24 (4.7%)
[†] Median (Range); n (%)	

Proportion of high-PD1 among cancer types (Figure 1)



Univariable logistic regression (Table 1)

```
dat <-
  roo %>% select(`PD-1`, BTLA, CTLA4, LAG3, NECTIN2, `PD-L1`, `PD-L2`, PVR, TIGIT, TNFRSF14, TIM3, VISTA,
    lung, colon, breast, ovarian, panc, uterine, net, sarcoma, melanoma, TMB10, Age, Gender, TMB20) %>%
  mutate_at(c(1:12), ~if_else(>=75,1,0)) %>%
  mutate_at("Age", ~if_else(>=median(.), 1, 0)) %>%
  rename(Aged=Age)

weel <-
  dat %>%
  dplyr::select(Aged, Gender, `PD-1`, BTLA, CTLA4, LAG3, NECTIN2, `PD-L1`, `PD-L2`, PVR, TIGIT,
    TIM3, TNFRSF14, VISTA, lung, colon, breast, ovarian, panc, uterine, sarcoma, melanoma,
    TMB10, TMB20) %>%
  tbl_uvregression(
    .,
    method = glm,
    y = `PD-1`,
    method.args = list(family = binomial),
    exponentiate = TRUE,
    pvalue_fun = ~style_pvalue(.x, digits = 3)
  )
weel
```

Characteristic	N	OR ¹	95% CI ¹	p-value
Aged	514	1.34	0.85, 2.11	0.208
Gender	514			
Female		—	—	

¹OR = Odds Ratio, CI = Confidence Interval

Characteristic	N	OR [†]	95% CI [†]	p-value
Male		0.90	0.56, 1.42	0.655
BTLA	514	9.48	5.72, 15.9	<0.001
CTLA4	514	16.3	9.54, 28.4	<0.001
LAG3	514	10.4	6.32, 17.3	<0.001
NECTIN2	514	0.77	0.47, 1.23	0.281
PD-L1	514	6.26	3.61, 10.9	<0.001
PD-L2	514	5.85	3.57, 9.63	<0.001
PVR	514	0.88	0.55, 1.41	0.614
TIGIT	514	31.3	17.8, 56.9	<0.001
TIM3	514	3.76	2.25, 6.23	<0.001
TNFRSF14	514	2.31	1.39, 3.78	0.001
VISTA	514	3.06	1.93, 4.86	<0.001
lung	514	0.79	0.18, 2.42	0.715
colon	514	0.85	0.50, 1.41	0.549
breast	514	0.87	0.37, 1.84	0.736
ovarian	514	0.87	0.35, 1.91	0.747
panc	514	1.30	0.63, 2.51	0.449
uterine	514	1.20	0.39, 3.08	0.721
sarcoma	514	0.63	0.15, 1.89	0.470
melanoma	514	4.64	0.85, 25.4	0.063
TMB10	450	1.20	0.44, 2.85	0.694
TMB20	450	2.05	0.44, 7.27	0.299

[†] OR = Odds Ratio, CI = Confidence Interval

Multivariable logistic regression

```
var <-
  wee1$table_body %>% filter(p.value < 0.05) %>% .$variable
hoge <- str_c(var, collapse = "` + `") # combining 10 variables for formula
hoge <- str_c("`", hoge, "`")
formula <- str_c("`PD-1`", " ~ ", hoge) %>% as.formula() # combining right-hand-side to left hand side with "~"
formula
```

```
## `PD-1` ~ BTLA + CTLA4 + LAG3 + `PD-L1` + `PD-L2` + TIGIT + TIM3 +
## TNFRSF14 + VISTA
## <environment: 0x000001e991a9f118>
```

```
roo %>% select(`PD-1`, all_of(var)) %>%
  mutate(across(.cols = c(1:10), ~if_else(.>=75,1,0))) %>%
  glm(formula, data = ., family = "binomial") %>%
```

```
tbl_regression(exponentiate = TRUE,
               pvalue_fun = ~style_pvalue(.x, digits = 3))
```

Characteristic	OR ¹	95% CI ¹	p-value
BTLA	0.98	0.40, 2.24	0.960
CTLA4	3.44	1.54, 7.60	0.002
LAG3	4.14	2.05, 8.34	<0.001
PD-L1	0.85	0.31, 2.21	0.745
PD-L2	2.25	0.96, 5.20	0.059
TIGIT	11.1	4.92, 26.2	<0.001
TIM3	0.51	0.20, 1.21	0.138
TNFRSF14	1.13	0.52, 2.41	0.750
VISTA	1.43	0.71, 2.84	0.313

¹OR = Odds Ratio, CI = Confidence Interval

Calculating proportion of patients who had high PD-1 expression

```
## defining function to strictly round numbers
strict_round <- function(x, digits = 0){
  shift <- 10^digits
  rounded <- floor(x * shift + 0.5) / shift
  return(rounded)
}
```

```
## defining function to summarize the number of high expression patients
group_and_summarize <- function(df, column_name) {
  result <- df %>%
    group_by(!sym(column_name)) %>%
    summarise(n = n(), high = sum(`PD-1`, na.rm = TRUE)) %>%
    mutate(prop = strict_round(100 * high / n, 0)) %>%
    mutate(PROP = str_c(prop, "% [", high, "/", n, "]")) %>%
    mutate(name = column_name, .before=!sym(column_name)) %>%
    rename(hoge = !sym(column_name)) %>%
    mutate(hoge = hoge %>% as.character())

  return(result)
}
```

```
dat1 <-
  dat %>% mutate(male1 = if_else(.$Gender=="Male",1,0)) %>%
  select(-Gender)

all_columns <- setdiff(names(dat1), "PD-1")

results_list <- lapply(all_columns, function(col) group_and_summarize(dat1, col))
combined_tibble <- bind_rows(results_list)
combined_tibble %>% select(-c(3:5)) %>% drop_na() %>% rename(var=name, condition=hoge) %>%
  pivot_wider(names_from = var, values_from = condition) %>%
  mutate(across(2:12, ~ifelse(==1,"u226575", "<75"))) %>%
  mutate(across(13:21, ~ifelse(==1,"Yes", "No"))) %>%
  mutate(across(22, ~ifelse(==1,"u226510", "<10"))) %>%
  mutate(across(23, ~ifelse(==1,"u226561", "<61"))) %>%
  mutate(across(24, ~ifelse(==1,"u226520", "<20"))) %>%
  mutate(across(25, ~ifelse(==1,"Male", "Female"))) %>%
```

```
pivot_longer(cols = -PROP) %>% drop_na(value) %>%
rename(condition = value, variable = name, proportion = PROP) %>%
select(2,3,1) %>% DT::datatable()
```

Show 10 entries

Search:

	variable	condition	proportion
1	BTLA	<75	10% [43/418]
2	BTLA	≥75	52% [50/96]
3	CTLA4	<75	9% [39/427]
4	CTLA4	≥75	62% [54/87]
5	LAG3	<75	9% [35/398]
6	LAG3	≥75	50% [58/116]
7	NECTIN2	<75	20% [63/323]
8	NECTIN2	≥75	16% [30/191]
9	PD-L1	<75	13% [60/447]
10	PD-L1	≥75	49% [33/67]

Showing 1 to 10 of 48 entries

Previous

1

2

3

4

5

Next

Survival Analysis

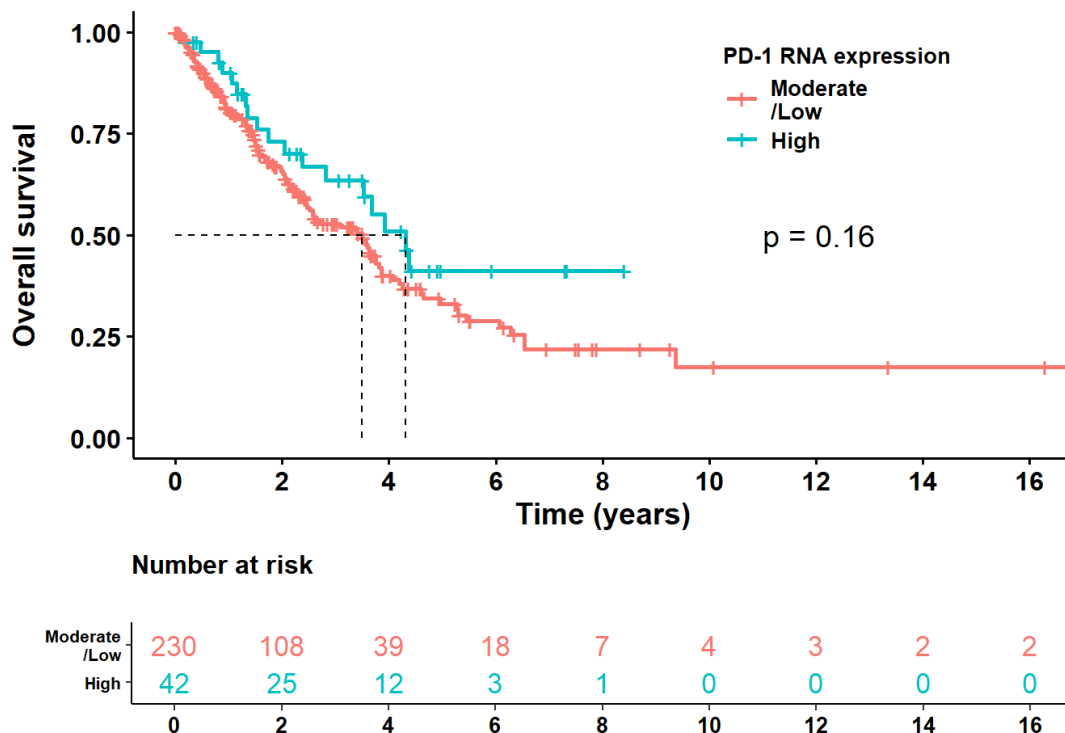
Making subset of non-immunotherapy and immunotherapy group

```
roo_imu <-
  roo %>% filter(I0==1) %>%
  filter(!is.na(`OS from Dx date`))
roo_never <-
  roo %>% filter(I0==0) %>%
  filter(!is.na(`OS from Dx date`))
```

Patients who never received immunotherapy

```
Yn <- Surv(roo_never$`OS from Dx date`,
           roo_never$`OS event`)
Zn <- survival::survfit(Yn ~ roo_never$PD1_high)
survminer::ggsurvplot(Zn, roo_never, risk.table = T,
  #title="Patinets who never received immunotherapy (N=272) from the date of metastatic disease",
  break.time.by=2,
  font.title = c("bold"),
  font.x = c("bold"),
  font.y = c("bold"),
  font.tickslab = c("bold"),
  ylab="Overall survival", xlab="Time (years)",
  surv.median.line=c("hv"),
  risk.table.col = "strata",risk.table.height=0.3,
  legend.title="PD-1 RNA expression",
  legend = c(0.75,0.8),
  pval = T, pval.coord=c(11,0.5),
  legend.labs = c("Moderate\nLow", "High")
) -> pn
```

```
pn$plot <- pn$plot + theme(legend.title = element_text(face="bold", size=10, color = "black"),
  legend.text = element_text(face="bold", size=10, color = "black"))
pn$table <- pn$table + labs(x="", subtitle="") + theme_classic() +
  theme(title = element_text(face="bold", size=10,color = "black"),
    axis.text.x = element_text(face="bold", size=10,color = "black"),
    axis.text.y = element_text(face="bold", size=8,color = "black"),
    axis.title.y = element_blank()
  )
pn
```



```
fit1n <- surv_fit(Surv(`OS from Dx date`, `OS event`) ~ PD1_high, data = roo_never)
surv_median(fit1n)
```

```
## Warning: `select_()` was deprecated in dplyr 0.7.0.
## Please use `select()` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was generated.
```

```
##      strata median lower upper
## 1 PD1_high=0  3.499 2.508 3.849
## 2 PD1_high=1  4.312 2.806  NA
```

```
survdif(Surv(roo_never$`OS from Dx date`,
  roo_never$`OS event`) ~ roo_never$PD1_high) -> results
results$pvalue
```

```
## [1] 0.1645739
```

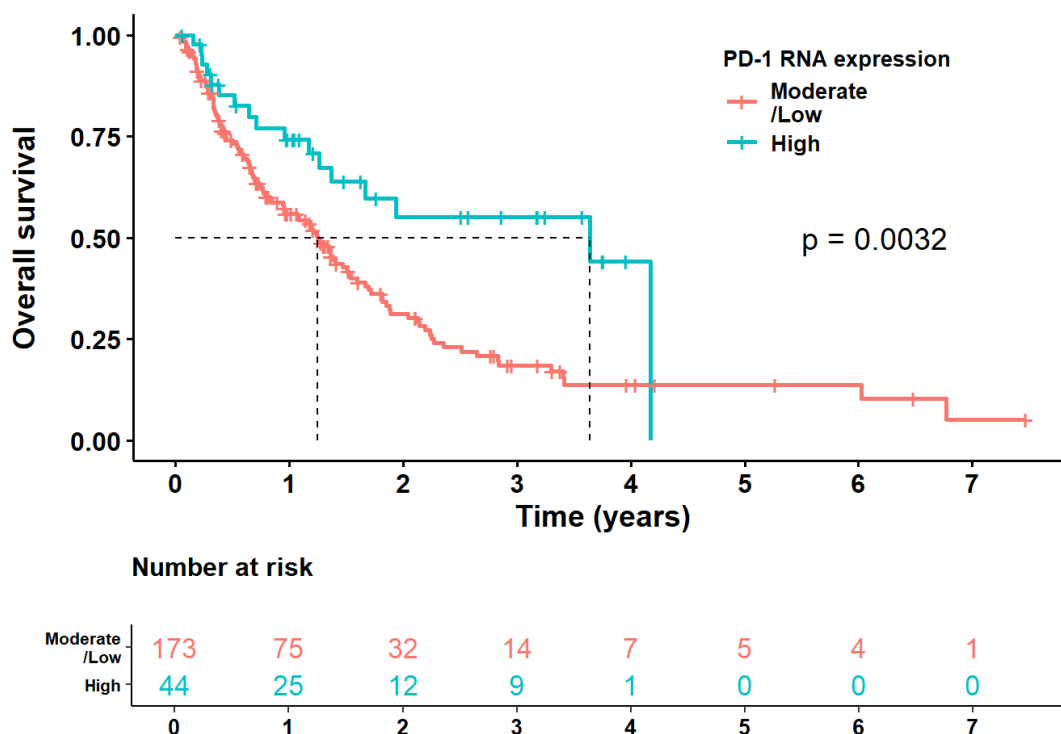
```
coxph(Yn ~ PD1_high, data = roo_never) %>%
  broom::tidy(exponentiate=T, conf.int=T) %>% select(1,2,6,7,5)
```

```
## # A tibble: 1 x 5
##   term      estimate conf.low conf.high p.value
```

```
## <chr> <dbl> <dbl> <dbl> <dbl>
## 1 PD1_high 0.704 0.428 1.16 0.167
```

PFS and OS from the start date of immunotherapy

```
Yg <- Surv(roo_imu$`OS from IO date`,
           roo_imu$`OS event`)
Zg <- survival::survfit(Yg ~ roo_imu$PD1_high)
survminer::ggsurvplot(Zg, roo_imu, risk.table = T,
                      #title="Patients who received immunotherapy (N=217) from the start date of ICI",
                      break.time.by=1,
                      xlim=c(0,7.5),
                      font.title = c("bold"),
                      font.x = c("bold"),
                      font.y = c("bold"),
                      font.tickslab = c("bold"),
                      ylab="Overall survival", xlab="Time (years)",
                      surv.median.line=c("hv"),
                      risk.table.col = "strata",risk.table.height=0.3,
                      legend.title="PD-1 RNA expression",
                      legend = c(0.75,0.8),
                      pval = T, pval.coord=c(5.5,0.5),
                      legend.labs = c("Moderate\n/Low", "High")
                      ) -> pg
pg$plot <- pg$plot + theme(legend.title = element_text(face="bold", size=10, color = "black"),
                          legend.text = element_text(face="bold", size=10, color = "black"))
pg$table <- pg$table + labs(x="", subtitle="") + theme_classic() +
  theme(title = element_text(face="bold", size=10,color = "black"),
        axis.text.x = element_text(face="bold", size=10,color = "black"),
        axis.text.y = element_text(face="bold", size=8,color = "black"),
        axis.title.y = element_blank()
  )
pg
```



```
fit1n <- surv_fit(Surv(`OS from Dx date`, `OS event`) ~ PD1_high, data = roo_imu)
surv_median(fit1n)
```

```
##           strata median lower upper
## 1 PD1_high=0  2.691 2.264 3.877
## 2 PD1_high=1  3.869 2.604   NA
```

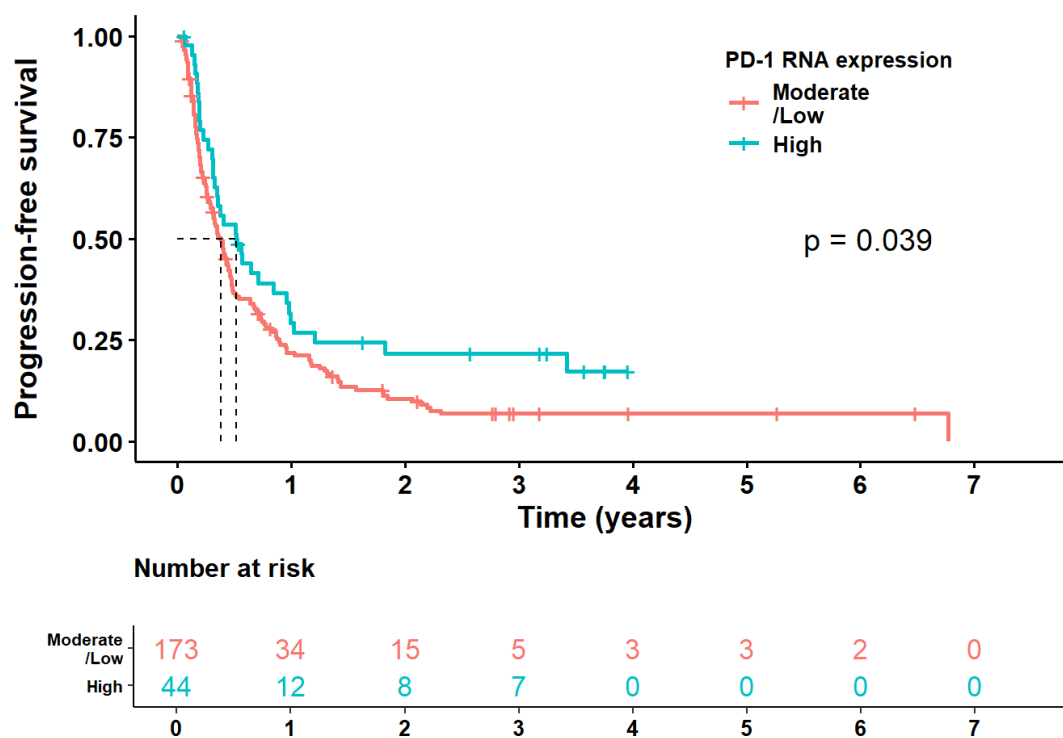
```
survdifff(Surv(roo_imu$`OS from IO date`,
               roo_imu$`OS event`) ~ roo_imu$PD1_high) -> results
results$pvalue # Log-rank p from survdiff()
```

```
## [1] 0.003186236
```

```
coxph(Yg ~ PD1_high, data = roo_imu) %>%
  broom::tidy(exponentiate=T, conf.int=T) %>% select(1,2,6,7,5)
```

```
## # A tibble: 1 x 5
##   term      estimate conf.low conf.high p.value
##   <chr>      <dbl>   <dbl>   <dbl>   <dbl>
## 1 PD1_high    0.471     0.282     0.786 0.00394
```

```
Yp <- Surv(roo_imu$`PFS from IO date`,
           roo_imu$`PFS event`)
Zp <- survival::survfit(Yp ~ roo_imu$PD1_high)
survminer::ggsurvplot(Zp, roo_imu, risk.table = T,
                      break.time.by=1,
                      xlim=c(0,7.5),
                      font.title = c("bold"),
                      font.x = c("bold"),
                      font.y = c("bold"),
                      font.tickslab = c("bold"),
                      ylab="Progression-free survival", xlab="Time (years)",
                      surv.median.line=c("hv"),
                      risk.table.col = "strata", risk.table.height=0.3,
                      legend.title="PD-1 RNA expression",
                      legend = c(0.75,0.8),
                      pval = T, pval.coord=c(5.5,0.5),
                      legend.labs = c("Moderate\n/Low", "High")
                      ) -> ppg
ppg$plot <- ppg$plot + theme(legend.title = element_text(face="bold", size=10, color = "black"),
                           legend.text = element_text(face="bold", size=10, color = "black"))
ppg$table <- ppg$table + labs(x="", subtitle="") + theme_classic() +
  theme(title = element_text(face="bold", size=10,color = "black"),
        axis.text.x = element_text(face="bold", size=10,color = "black"),
        axis.text.y = element_text(face="bold", size=8,color = "black"),
        axis.title.y = element_blank()
  )
ppg
```



```
fit1p <- surv_fit(Surv(`PFS from IO date`, `PFS event`) ~ PD1_high, data = roo_imu)
surv_median(fit1p)
```

```
##      strata median lower upper
## 1 PD1_high=0  0.378 0.307 0.457
## 2 PD1_high=1  0.517 0.326 0.975
```

```
survdif(Surv(roo_imu$`PFS from IO date`,
             roo_imu$`PFS event`) ~ roo_imu$PD1_high) -> results
results$pvalue # Log-rank p from survdiff()
```

```
## [1] 0.03863058
```

```
coxph(Yp ~ PD1_high, data = roo_imu) %>%
  broom::tidy(exponentiate=T, conf.int=T) %>% select(1,2,6,7,5)
```

```
## # A tibble: 1 x 5
##   term      estimate conf.low conf.high p.value
##   <chr>      <dbl>    <dbl>    <dbl>    <dbl>
## 1 PD1_high    0.676    0.465    0.982    0.0400
```

OS Cox regression among 217 patients (Table 2)

Univariable

```
datcoxos <-
  roo_imu %>% select(Age, Gender,
                    BTLA, CTLA4, LAG3, NECTIN2, `PD-1`, `PD-L1`, `PD-L2`, PVR, TIGIT, TIM3, TNFRSF14, VISTA,
                    lung, colon, breast, ovarian, panc, uterine, net, sarcoma, melanoma,
                    TMB10, `OS from IO date`, `OS event`) %>%
  mutate_at(c(3:14), ~ifelse(.>=75,1,0)) %>%
  mutate(age61 = ifelse(Age>=median(floor(Age)), 1,0)) %>%
```

```
select(age61, 2:26)
xox217 <-
tbl_uvregression(
  data = datcoxos,
  method = coxph,
  y = Surv(`OS from IO date`, `OS event`),
  exponentiate = TRUE,
  pvalue_fun = ~style_pvalue(.x, digits = 3)
)
xox217
```

Characteristic	N	HR ¹	95% CI ¹	p-value
age61	217	1.05	0.75, 1.48	0.773
Gender	217			
Female		—	—	
Male		1.09	0.77, 1.54	0.612
BTLA	217	0.42	0.24, 0.73	0.002
CTLA4	217	0.44	0.26, 0.74	0.002
LAG3	217	0.50	0.32, 0.79	0.003
NECTIN2	217	1.51	1.05, 2.17	0.028
PD-1	217	0.47	0.28, 0.79	0.004
PD-L1	217	0.58	0.33, 1.01	0.054
PD-L2	217	0.59	0.38, 0.92	0.020
PVR	217	1.59	1.10, 2.30	0.013
TIGIT	217	0.50	0.30, 0.85	0.010
TIM3	217	0.50	0.31, 0.80	0.004
TNFRSF14	217	0.59	0.37, 0.97	0.036
VISTA	217	0.96	0.66, 1.41	0.853
lung	217	0.90	0.47, 1.74	0.762
colon	217	1.70	1.16, 2.49	0.007
breast	217	0.85	0.45, 1.63	0.632
ovarian	217	1.04	0.59, 1.85	0.882
panc	217	1.70	0.92, 3.16	0.093
uterine	217	0.72	0.31, 1.62	0.423
net	217	0.81	0.26, 2.55	0.719
sarcoma	217	0.49	0.20, 1.22	0.125
melanoma	217	0.35	0.09, 1.43	0.144
TMB10	191	0.59	0.32, 1.07	0.083
¹ HR = Hazard Ratio, CI = Confidence Interval				

Multivariable

```
xox217$table_body %>% filter(p.value <= 0.1) %>% .$variable -> var1
hoge1 <- str_c(var1, collapse = "` + `") # combining 10 variables for formula
hoge1 <- str_c("`", hoge1, "`")
formula1 <- str_c("surv_1", " ~ ", hoge1) %>% as.formula() # combining right-hand-side to left hand side with "~"
surv_1 <- Surv(datcoxos$`OS from IO date`, datcoxos$`OS event`)

fit.coxphdn <- coxph(formula1, data = datcoxos)
fit.coxphdn %>%
  tbl_regression(exponentiate = T,
                 estimate_fun = function(x) style_number(x, digits = 2),
                 pvalue_fun = ~style_pvalue(.x, digits = 3))
```

Characteristic	HR [†]	95% CI [†]	p-value
BTLA	0.56	0.22, 1.40	0.211
CTLA4	0.88	0.41, 1.92	0.753
LAG3	0.92	0.52, 1.64	0.780
NECTIN2	1.50	1.00, 2.24	0.048
PD-1	0.40	0.18, 0.92	0.030
PD-L1	0.59	0.27, 1.31	0.195
PD-L2	1.26	0.63, 2.52	0.511
PVR	1.27	0.84, 1.93	0.261
TIGIT	2.64	0.98, 7.12	0.056
TIM3	0.46	0.21, 1.01	0.053
TNFRSF14	0.82	0.45, 1.49	0.514
colon	1.72	1.12, 2.65	0.014
panc	2.36	1.06, 5.25	0.035
TMB10	0.50	0.27, 0.96	0.036

[†]HR = Hazard Ratio, CI = Confidence Interval

PFS Cox regression (Table 3)

Univariable

```
datcoxpfps <-
  roo_imu %>% select(Age, Gender,
                    BTLA, CTLA4, LAG3, NECTIN2, `PD-1`, `PD-L1`, `PD-L2`, PVR, TIGIT, TIM3, TNFRSF14, VISTA,
                    lung, colon, breast, ovarian, panc, uterine, net, sarcoma, melanoma,
                    TMB10, `PFS from IO date`, `PFS event`) %>%
  mutate_at(c(3:14), ~ifelse(.>=75,1,0)) %>%
  mutate(age61 = ifelse(Age>=median(floor(Age)), 1,0)) %>%
  select(age61, 2:26)

pop217 <-
  tbl_uvregression(
    data = datcoxpfps,
    method = coxph,
    y = Surv(`PFS from IO date`, `PFS event`),
    exponentiate = TRUE,
    pvalue_fun = ~style_pvalue(.x, digits = 3))
```

)
pop217

Characteristic	N	HR [†]	95% CI [†]	p-value
age61	217	0.77	0.58, 1.03	0.076
Gender	217			
Female		—	—	
Male		1.12	0.84, 1.49	0.454
BTLA	217	0.59	0.39, 0.90	0.015
CTLA4	217	0.58	0.39, 0.87	0.009
LAG3	217	0.77	0.54, 1.09	0.134
NECTIN2	217	1.19	0.87, 1.61	0.273
PD-1	217	0.68	0.47, 0.98	0.040
PD-L1	217	0.86	0.58, 1.27	0.455
PD-L2	217	0.78	0.55, 1.11	0.172
PVR	217	1.39	1.03, 1.89	0.034
TIGIT	217	0.76	0.52, 1.13	0.179
TIM3	217	0.79	0.55, 1.13	0.192
TNFRSF14	217	0.71	0.48, 1.05	0.086
VISTA	217	0.89	0.64, 1.23	0.476
lung	217	0.94	0.52, 1.68	0.827
colon	217	1.20	0.86, 1.67	0.295
breast	217	1.04	0.62, 1.73	0.890
ovarian	217	1.08	0.65, 1.81	0.759
panc	217	1.40	0.82, 2.38	0.213
uterine	217	0.76	0.40, 1.45	0.409
net	217	0.98	0.36, 2.65	0.972
sarcoma	217	0.61	0.30, 1.24	0.169
melanoma	217	0.51	0.19, 1.37	0.180
TMB10	191	0.63	0.38, 1.04	0.072
[†] HR = Hazard Ratio, CI = Confidence Interval				

Multivariable

```
pop217$table_body %>% filter(p.value <= 0.1) %>% .$variable -> var2
hoge2 <- str_c(var2, collapse = " + ") # combining 10 variables for formula
hoge2 <- str_c("`", hoge2, "`")
formula2 <- str_c("surv_2", " ~ ", hoge2) %>% as.formula() # combining right-hand-side to left hand side with "~"
surv_2 <- Surv(datcoxpf$`PFS from IO date`, datcoxpf$`PFS event`)
formula2
```

```
## surv_2 ~ age61 + BTLA + CTLA4 + `PD-1` + PVR + TNFRSF14 + TMB10
## <environment: 0x000001e99660c330>
```

```
fit.coxphp <- coxph(formula2, data = datcoxpsfs)
fit.coxphp %>%
  tbl_regression(exponentiate = T,
    estimate_fun = function(x) style_number(x, digits = 2),
    pvalue_fun = ~style_pvalue(.x, digits = 3))
```

Characteristic	HR [†]	95% CI [†]	p-value
age61	0.78	0.57, 1.06	0.111
BTLA	0.77	0.38, 1.57	0.475
CTLA4	0.65	0.32, 1.31	0.230
PD-1	0.93	0.54, 1.59	0.778
PVR	1.24	0.89, 1.73	0.198
TNFRSF14	0.90	0.58, 1.41	0.648
TMB10	0.69	0.41, 1.15	0.153

[†]HR = Hazard Ratio, CI = Confidence Interval

Counting the number of patients who were analyzed in Cox regression

```
roo_imu %>% filter(!is.na(`OS from Dx date`)) %>%
  select(Age, Gender, BTLA, CTLA4, LAG3, NECTIN2, `PD-1`, `PD-L1`, `PD-L2`, PVR, TIGIT, TIM3, TNFRSF14, VISTA,
    lung, colon, breast, ovarian, panc, uterine, net, sarcoma, melanoma, TMB10) %>%
  mutate_at(c(3:14), ~ifelse(.>=75, 1, 0)) %>%
  mutate(age61 = ifelse(.$Age>=median(floor(Age)), 1, 0)) %>%
  select(-Age) %>%
  summarise_all(~list(table(.) %>% as.data.frame(.))) %>%
  pivot_longer(everything()) %>%
  unnest(value) %>%
  pivot_wider(names_from = name, values_from = ".") %>%
  mutate(across(3:14, ~ifelse(==1, "\u226575", "<75"))) %>%
  mutate(across(15:23, ~ifelse(==1, "Yes", "No"))) %>%
  mutate(across(24, ~ifelse(==1, "\u226510", "<10"))) %>%
  mutate(across(25, ~ifelse(==1, "\u226561", "<61"))) %>%
  pivot_longer(cols = -Freq) %>% drop_na(value) %>%
  rename(condition = value, variable = name, N = Freq) %>%
  select(2, 3, 1) %>% DT::datatable()
```

Show10▼entries

Search:

	variable	condition	N
1	Gender	Female	122
2	Gender	Male	95
3	BTLA	<75	181
4	PD-L1	<75	181
5	BTLA	≥75	36
6	PD-L1	≥75	36

	variable	condition	N
7	CTLA4	<75	176
8	CTLA4	≥75	41
9	LAG3	<75	166
10	PD-L2	<75	166

Showing 1 to 10 of 48 entries

Previous

1

2

3

4

5

Next

Administered agents in patients with IO

```
roo_imu %>% select(Administered_agent) %>%
  mutate(across(1, ~ifelse(=="TSR-042", "Dostarlimab",.))) %>%
  mutate(across(1, ~ifelse(=="Nivolumab+Ipilimumab", "Ipilimumab+nivolumab",.))) %>%
  gtsummary::tbl_summary()
```

Characteristic	N = 217 ¹
Administered_agent	
Atezolizumab	10 (4.6%)
Avelumab	2 (0.9%)
cemipilimab	1 (0.5%)
Dostarlimab	1 (0.5%)
Durvalumab	6 (2.8%)
Ipilimumab	2 (0.9%)
Ipilimumab+nivolumab	14 (6.5%)
Ipilimumab+pembrolizumab	2 (0.9%)
nivolumab	51 (24%)
Pembrolizumab	128 (59%)
¹ n (%)	