

Figure S1. Plot of log (-log (progression-free survival ratio)) versus log (days of progression-free survival).

Hazard proportionality was tested by the parallelism between the curve of rs671(−) (cases with *ALDH2\*1/\*1*) and rs671(+) (cases with *ALDH22\*1/\*2* and *ALDH2\*2/\*2*) to examine the suitability for the Cox proportional hazard model.

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| Table S1. Immune-related adverse events (IrAEs) and second or subsequent ICI doses. | | | | | | | |
|  | Total | | Rs671(−) | | Rs671(+) | | p |
| Diagnosis of IrAEs before disease progression\* | | | | | | | |
| Within 6 months | | | | | | | |
| No | 77 | (73%) | 39 | (70%) | 38 | (78%) | 0.361 |
| Yes | 28 | (27%) | 17 | (30%) | 11 | (22%) |  |
| ―Days from ICI, median (IQR) | 77 | (50–118) | 77 | (55–123) | 65 | (16–91) | 0.359 |
| Within a year | | | | | | | |
| No | 72 | (69%) | 36 | (64%) | 36 | (73%) | 0.312 |
| Yes | 33 | (31%) | 20 | (36%) | 13 | (27%) |  |
| ―Days from ICI, median (IQR) | 80 | (55–150) | 89 | (56–159) | 80 | (46–135) | 0.461 |
| Number of ICI doses during the entire observation period | | | | | | | |
| 1–5 | 50 | (48%) | 19 | (34%) | 31 | (63%) | **0.003** |
| 6–68 | 55 | (52%) | 37 | (66%) | 18 | (37%) |  |

Rs671(−); *ALDH2\*1/\*1*, rs671(+); *ALDH2\*1/\*2* or *ALDH2\*2/\*2*, ICI; immune checkpoint inhibitor, IQR; interquartile range. \*Prednisolone treatment for adverse events of ICIs or discontinuation of the ICI due to its adverse events. p; probability value for the Chi-squared test, Fisher’s exact test, or Wilcoxon rank-sum test. The hazard ratio (HR) of irAEs estimated by the Cox proportional hazard model also showed no difference between *ALDH2* genotypes. The HR of irAEs within 6 months for the rs671(+) group was 1.5 with a 95% confidence interval of 0.6–3.8. Similarly, the HR of irAEs within a year was 1.5 (0.6–3.6) (covariates: sex, age (continuous), Brinkman index (<100, <1000, ≥1000) (ordinal), type of first ICI, tumor histotype, TNM classification (categorical), number of lines (first, second, third, and later) (categorical), chemistry with ICI, PD-L1 positivity ratio (<1%, <50%, -100%, unassessed) (categorical), and *EGFR* mutation ((+), (-), unassessed) (categorical)).

SAS code for the Cox proportional hazards model using time-dependent explanatory variables

**proc** **phreg**;

class sex ici path stagec line chemo pdl1 egfr;

model pfsday\*pfs\_cens(**1**) = star2 sex age bi ici path stage line chemo pdl1 egfr aeStatus ae\_t;

if (aed = . or pfsday < aed) then do;

aeStatus = 0;

ae\_t = 0;

end;

else do;

aeStatus = 1;

ae\_t = aed;

end;

**run**;

star2; carrier of *ALDH2\*2* allele

bi; Brinkman Index

ici; type of immune checkpoint inhibitor (ICI)

path; tumor histotype

stage; TNM classification

line; Treatment line

chemo; chemotherapy with first ICI

pdl1; PD-L1 positive ratio in cancer tissue

egfr; *EGFR* mutation in cancer tissue

pfsday; period of progression-free survival

pfs\_cens; censored (1) or not censored (disease progressed, 0)

aeStatus; adverse effect of ICI (0 or 1) (time-dependent variable)

aed; days from starting ICI therapy to the diagnosis of adverse effects