Oncogene-driven regulation of adenosine pathway expression in multiple cancers
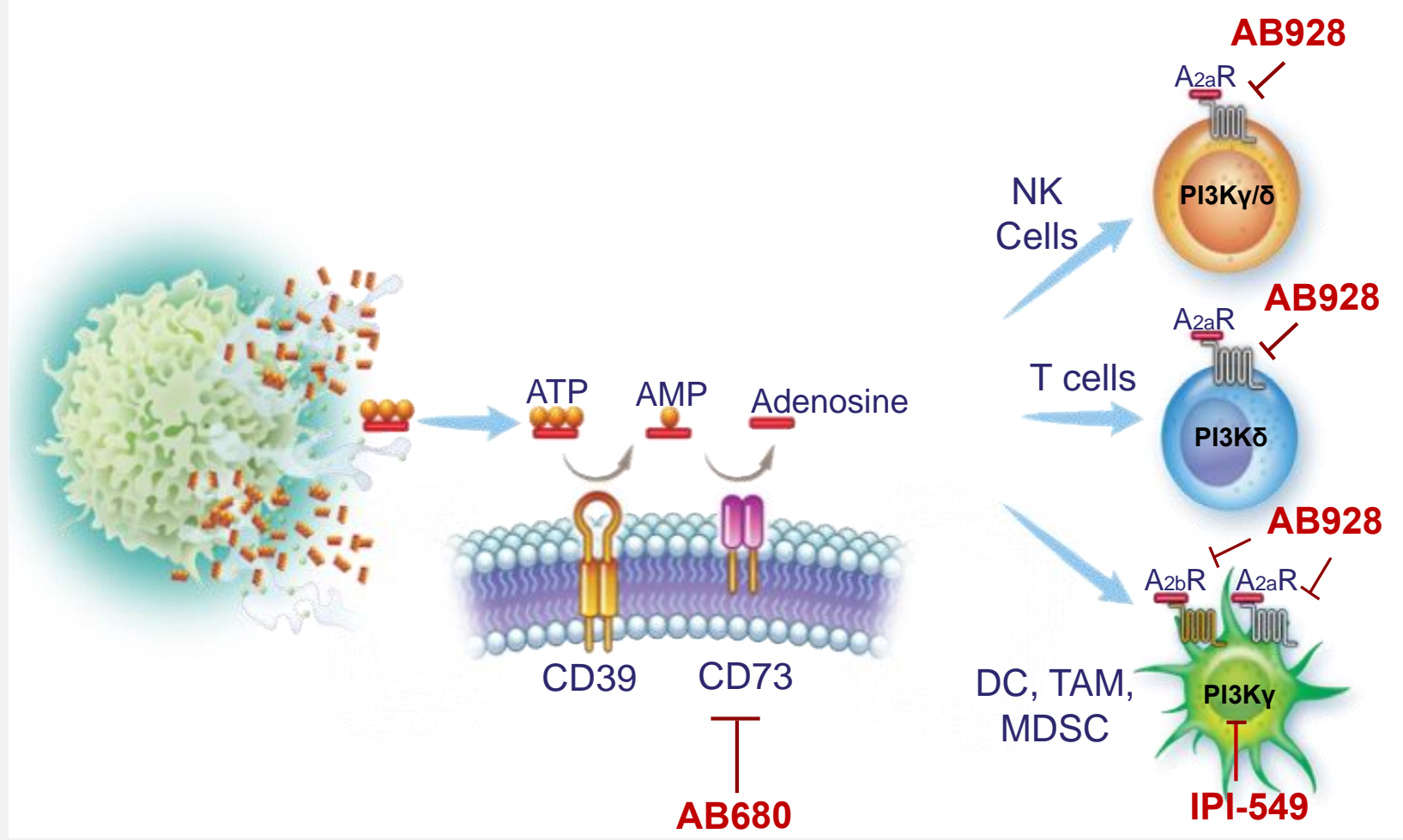
Udyavar AR, Piovesan D, Narasappa N, Lawson KV, Leleti MR, Young SW, Walters MJ, Tan JBL

Arcus Biosciences, Inc.; 3928 Point Eden Way, Hayward, CA 94545 (USA)

Introduction

- Previously, we have shown that AB928, a dual $A_{2a}R/A_{2b}R$ antagonist, and AB680, a potent selective inhibitor of CD73, rescue the immunosuppressive effects of adenosine in experimental tumor models.
- Oncogene-driven cancers tend to be non-responsive to PD(L)-1 inhibition. Herein we show that oncogenic alterations can modulate expression of genes of the adenosine pathway.

Materials and Methods

- **Pan-cancer TCGA dataset**: We used linear models adjusted for individual tumor types to assess if the expression of CD73 and adenosine pathway genes can be predicted by alterations in 299 consensus cancer driver genes (Bailey et.al Cell 2018) in pan-cancer TCGA dataset. We tested if CD73 expression is prognostic in the respective cancer driver mutant versus wild-type patients using Cox-regression models adjusted for tumor type.
- **NSCLC pembrolizumab cohort**: We associated pembrolizumab response in NSCLC (Rizvi et.al JCO 2018) with mutation status of cancer drivers strongly associated with CD73.
- For regression models, multiple testing correction was performed using Benjamini-Hochberg method. Stars indicate significant FDR (*** < 0.001,** <0.01,* < 0.2).
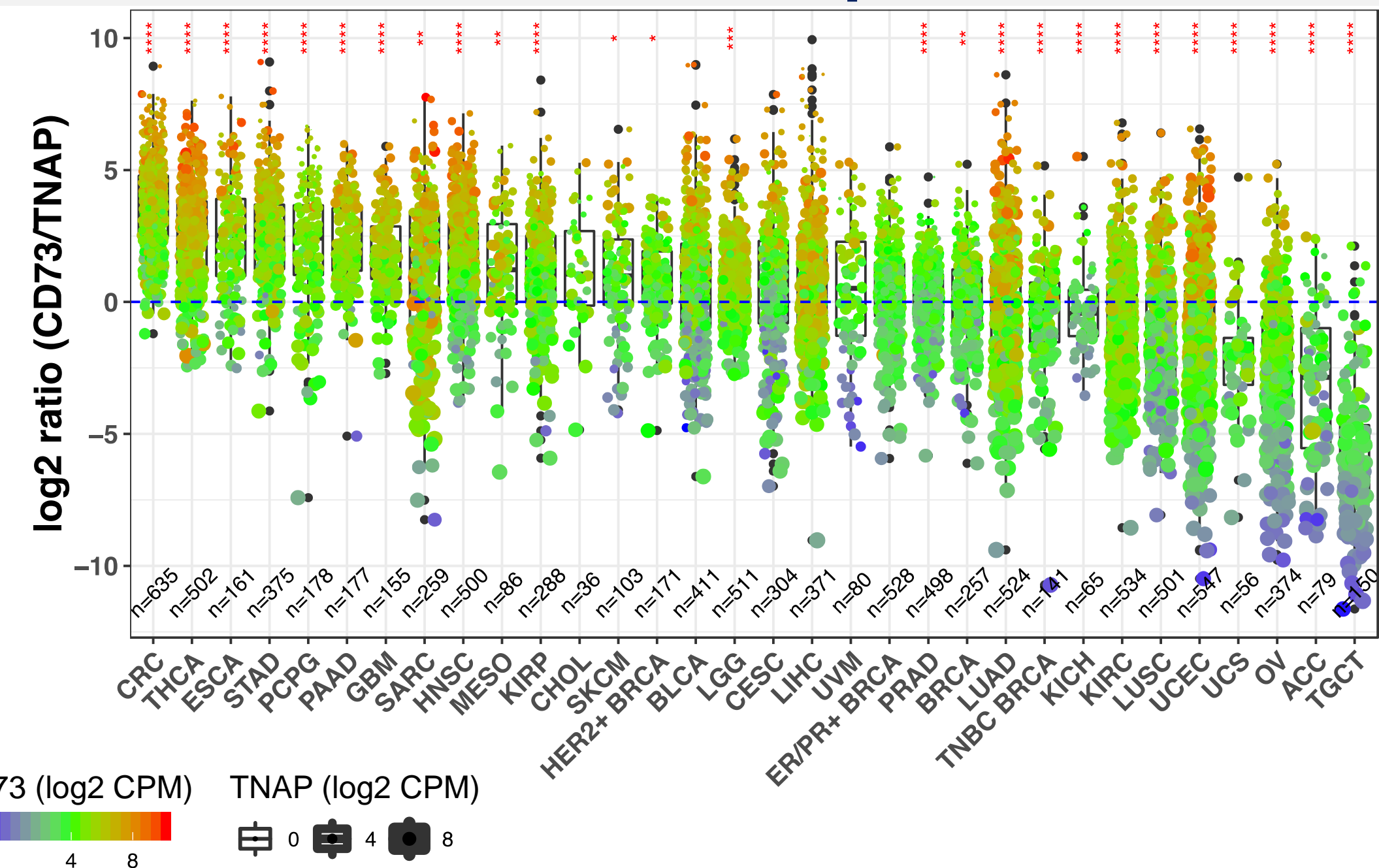
CD73/TNAP ratio across pan-cancer TCGA

Figure 1. CD73 and TNAP expression was derived from pan-cancer TCGA atlas dataset. Numbers indicate ratio of log2 CPM values for CD73 and TNAP. Tumors on left are high in CD73 and low in TNAP whereas tumors on right are high in TNAP and low in CD73.

Conclusions

- CD73 expression is strongly associated with mutations in several cancer driver genes independent of tumor type.
- In cancer driver wild-type patients, high CD73 expression is significantly associated with poor prognosis. In EGFR, MYC, PIK3CA/B, CDKN2A, PTEN, KLF5, TRAF3, FLT3, CYSLTR2 mutant patients, high CD73 expression is strongly associated with poor prognosis. Conversely, high CD73 expression strongly correlates with good prognosis in BRAF, PIK3R1, CIC, KMT2B mutant patients.
- Pembrolizumab response in NSCLC is associated with mutation status of oncogenic regulators that regulate CD73 expression. MYC, EGFR and PMS2 mutant patients have significantly poor prognosis associated with lower rate of durable clinical benefit with pembrolizumab treatment.
- Phase I clinical studies are ongoing for AB928 and AB680.

Discovery of oncogenic regulators of CD73 and adenosine pathway expression in pan-cancer TCGA
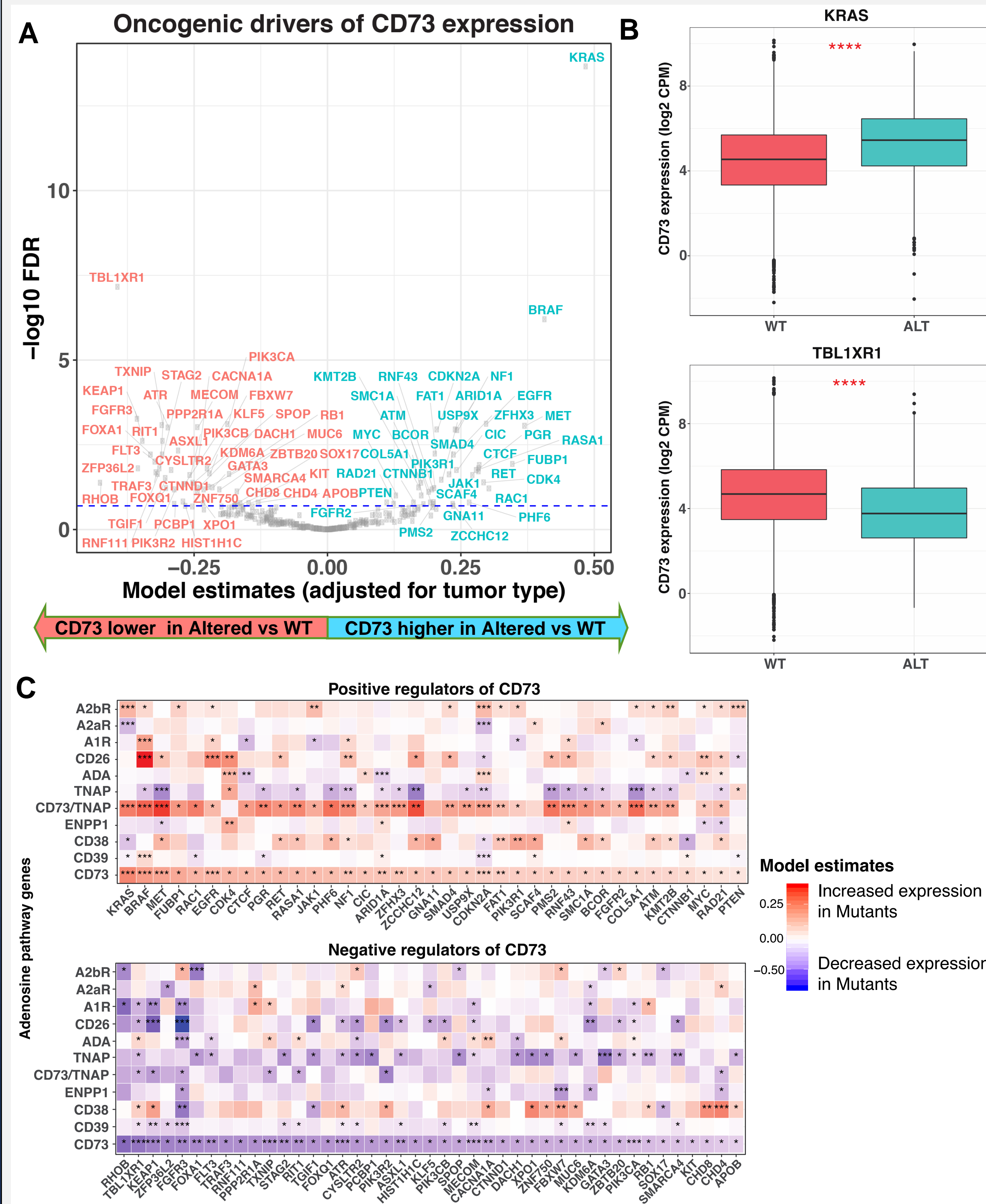
Figure 2. (A) Linear model estimates adjusted for tumor type of alterations in cancer driver genes that predict CD73 expression. (B) CD73 expression in representative examples of significant cancer drivers. (C) X-axis denotes the positive and negative regulators of CD73 from panel A. Y-axis shows linear model estimates adjusted for tumor type for each gene in the pathway.

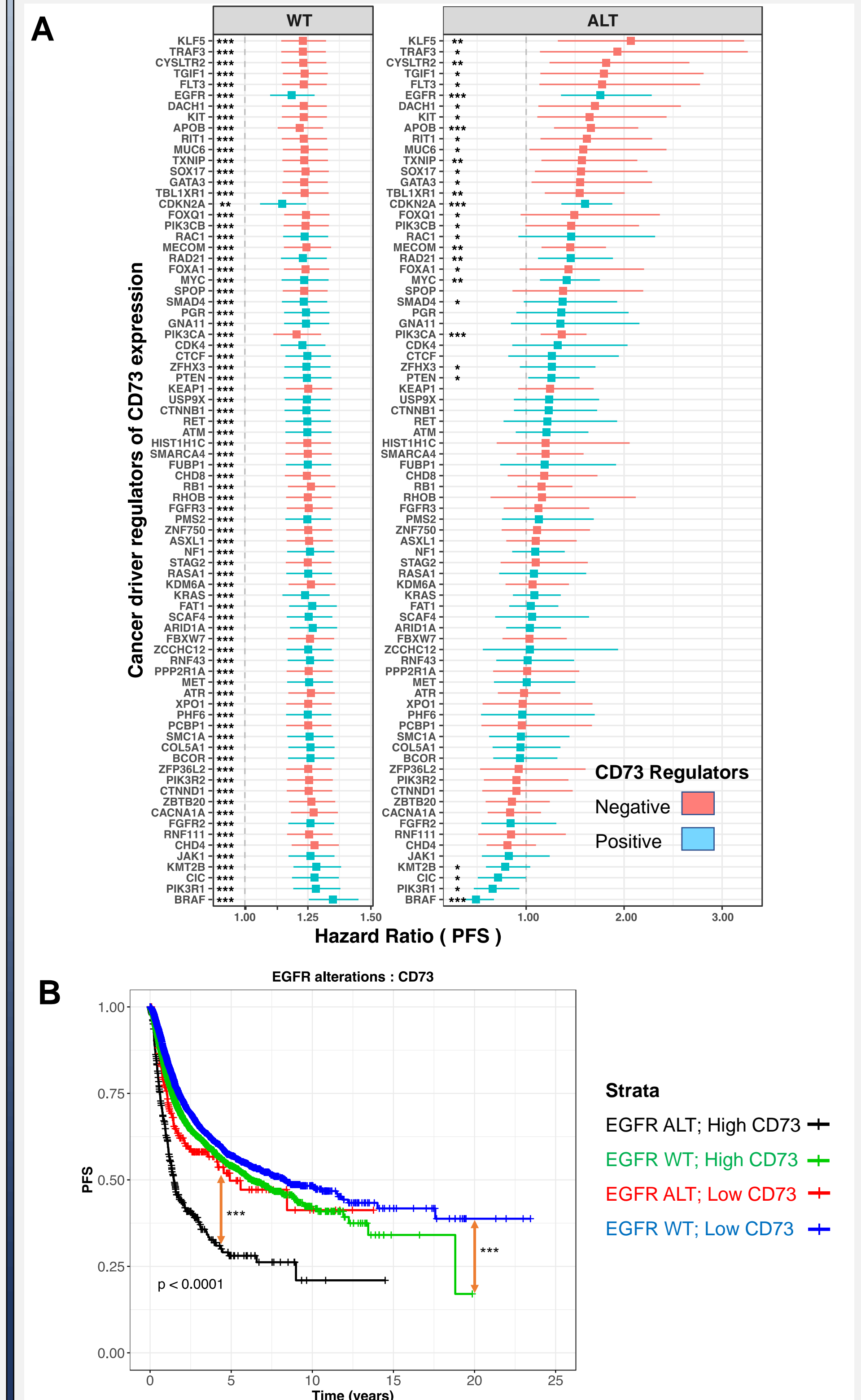## CD73 expression is prognostic in cancer driver mutant patients

Figure 3. (A) Forest plot shows hazard ratio with 95% confidence intervals adjusted for tumor type for CD73 expression in wild-type and mutated patients for each cancer driver for progression-free survival (PFS) in pan-cancer TCGA dataset. (B) Kaplan-Meier curve of CD73 expression in EGFR wild-type and mutant patients.

Association of pembrolizumab response and mutation status of cancer drivers regulating CD73 in NSCLC
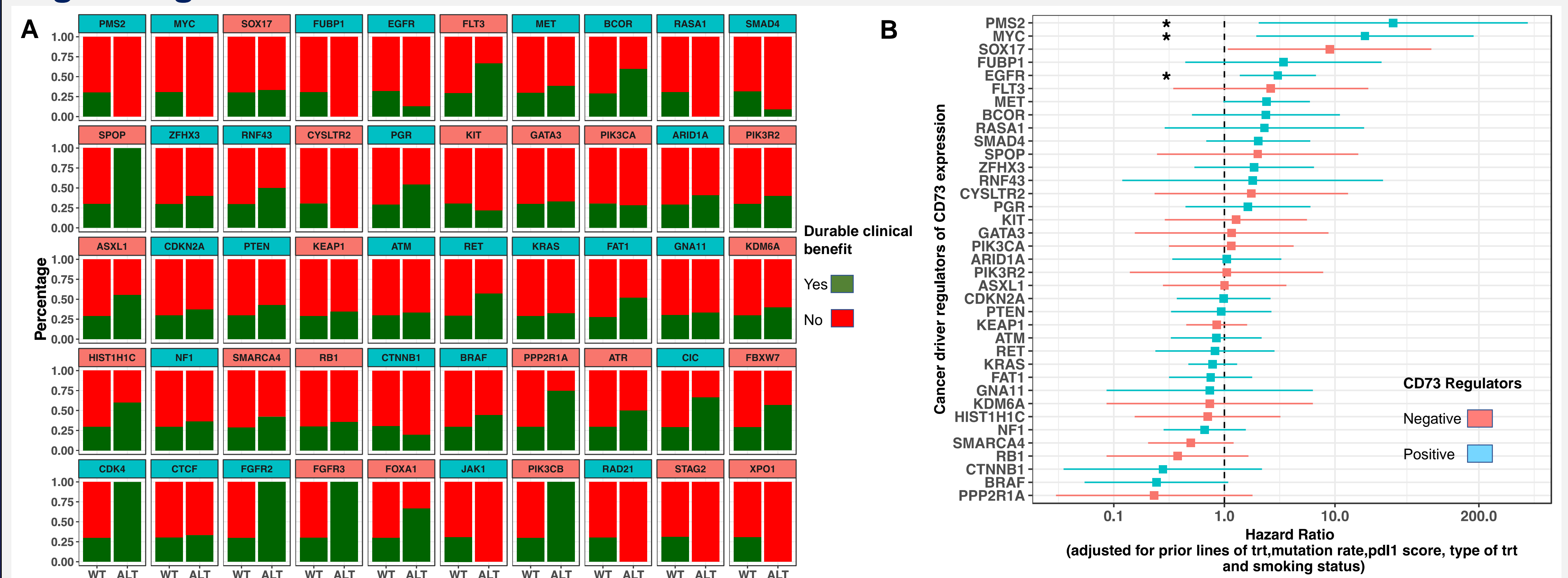
Figure 4. (A) Stacked barplot for cancer driver alterations positively and negatively associated with CD73 from Figure 1. Y-axis denotes percentage of patients that achieve or do not achieve durable clinical benefit beyond 6 months with pembrolizumab. (B) Forest plot of progression-free survival denoting hazard ratio (wild-type vs mutant) of cancer drivers that are positive and negative regulators of CD73.