The molecular landscape of PIWIL1 expression in colorectal adenocarcinoma (CRC).

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BACKGROUND

PIWIL1 is a cancer testis antigen overexpressed in solid tumors, particularly CRC, and is associated with advanced stage and poor prognosis. It is potentially a new therapeutic target, as PIWIL1 is not expressed in adult somatic tissue. A novel T cell receptor/PIWIL1 bispecific antibody is in development and restricted to individuals with human leukocyte antigen (HLA) A-02. We sought to characterize the molecular landscape of PIWIL1 in CRC.

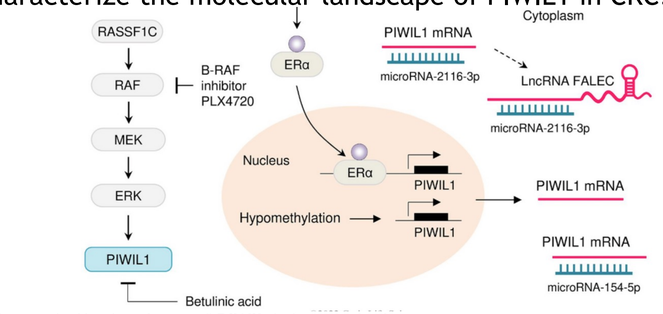


Figure 1: Mechanisms of PIWIL1 dysregulation From (Dong et al., 2021)

METHODS

26,581 CRC tumors were tested by next-generation sequencing (NGS) on DNA (592-gene or whole exome [WES]) and RNA (whole transcriptome [WTS]) at Caris Life Sciences (Phoenix, AZ). dMMR/MSI-H was tested by immunohistochemistry (IHC) and NGS respectively, HLA genotypes by WES and PD-L1 by IHC (SP142, 2+, 5% which was the threshold used for positivity). Tumor mutational burden (TMB) high was defined as ≥ 10 mt/Mb. RNA expression was used to estimate the tumor microenvironment using QuantiSEQ; T-cell inflamed score [TIS]) was used to predict immune checkpoint blockade (IO) response. The top (H) and bottom (L) quartiles of *PIWIL1* expression were compared using Chi-square/Fisher-Exact, and significance was determined as p adjusted for multiple comparisons (Q<0.05). Real-world overall survival (rwOS) was obtained from insurance claims and calculated from tissue collection to last contact.

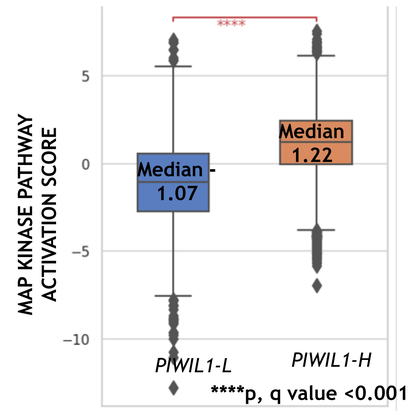
CONCLUSION

PIWIL1-H CRC is associated with higher rates of dMMR/MSI-H, TMB-H and PD-L1+ as well as IO-related gene expression and signatures that are predictive of response to IO. These data suggest the *PIWIL1*-H subpopulation could potentially derive substantial benefit from *PIWIL1*-targeted immunotherapy which should be evaluated in clinical trials.

RESULTS

Parameter	*PIWIL1-H*	*PIWIL1-L*
Sample Size	n=6645	n=6646
Median Age	65*	61
Gender (% female)	50.8%*	41.3%
LP/P Mutations *TP53*	81%*	69%
LP/P Mutations *KRAS*	53%*	41%
LP/P Mutations *BRAF*	16%*	3%
LP/P Mutations *PIK3CA*	14%	17%*
Genomic Loss of Heterozygosity	14%*	10%

Table 1: Patient Characteristics



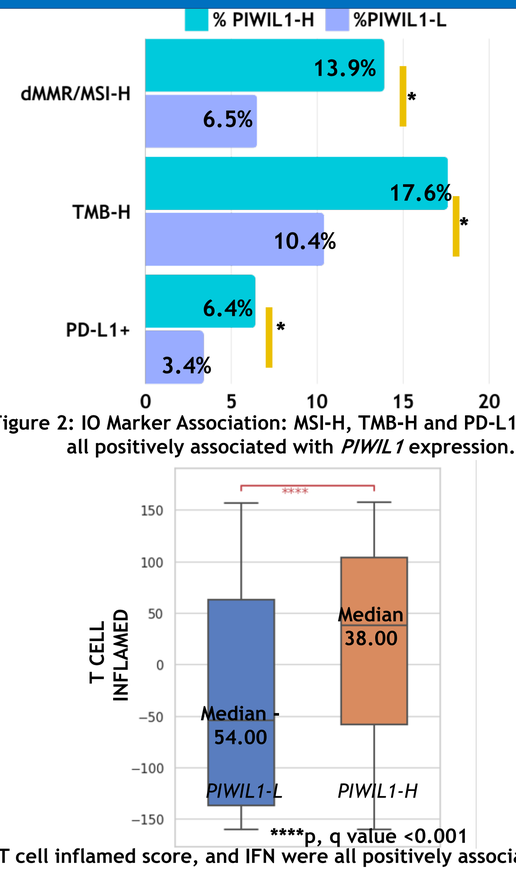


Figure 4: MAPK pathway activity score, T cell inflamed score, and IFN were all positively associated with *PIWIL1* expression. (p value, q value <0.001)

Figure 2: IO Marker Association: MSI-H, TMB-H and PD-L1-H were all positively associated with *PIWIL1* expression.

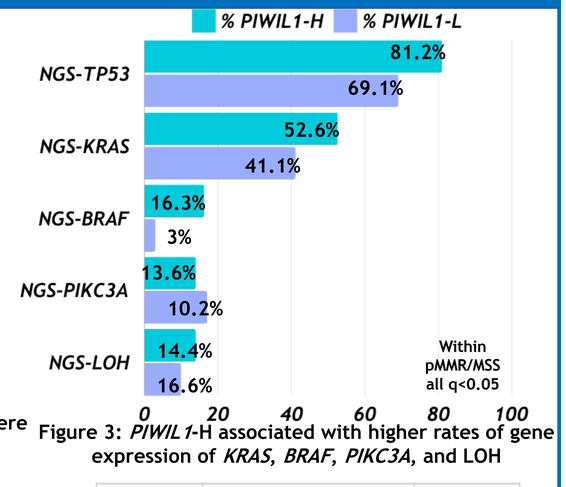
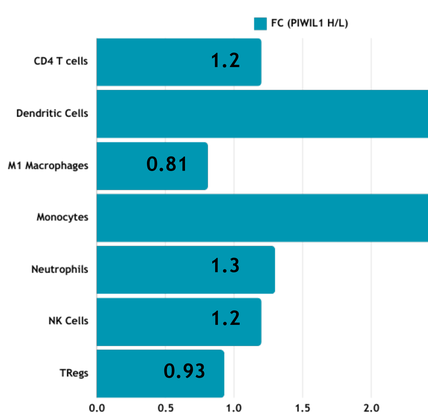


Figure 3: *PIWIL1*-H associated with higher rates of gene expression of *KRAS*, *BRAF*, *PIKC3A*, and LOH



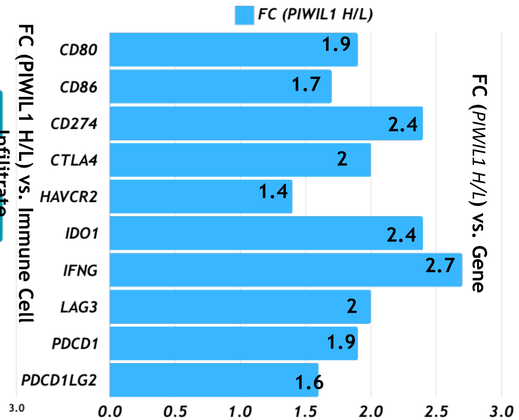


Figure 5: *PIWIL1* expression showed a positive association with infiltration of neutrophils, monocytes, CD4+T, dendritic and NK cells (FC: 1.3-2.9, Q<0.05) while Tregs and M1 macrophages had a negative association (0.8-0.9, Q<0.05).

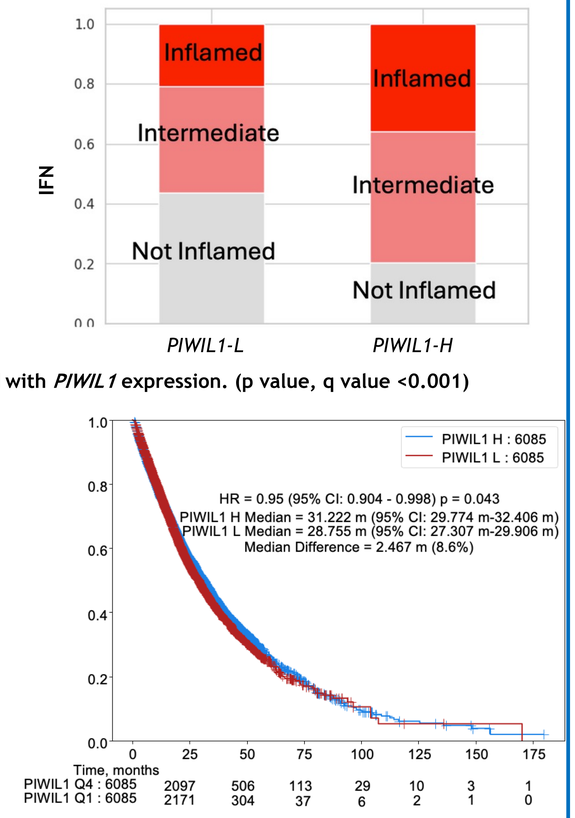


Figure 6: RwOS was evaluated from tissue collection to last contact. *PIWIL1*-H had a longer median OS than *PIWIL1*-L.