Molecular and immune landscape by cyclin dependent kinase (CDK) 4/6 expression and TP53 mutational status in mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) colorectal cancer (CRC)

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Introduction

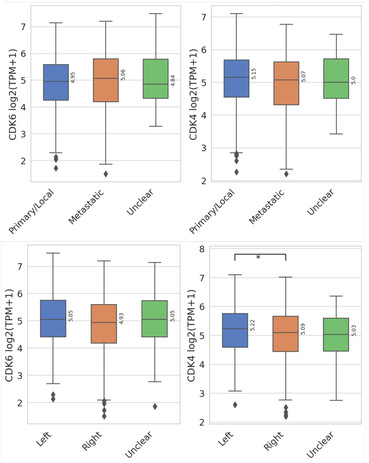
- CRC tumors that are dMMR/MSI-H may have a lower prevalence of *TP53* mutations compared to pMMR/MSS tumors.
- Some studies suggest that *TP53* mutated (*TP53*mt) MSI-H CRC has poorer response to immune checkpoint inhibitors (ICI) compared to *TP53* wild-type (*TP53*wt) tumors
- Cyclin-D kinases 4/6 (*CDK4/6*) play a role in cell cycle regulation and tumorigenesis. *CDK4/6* inhibition has been shown to have immunomodulatory effects on the tumor microenvironment (TME)
- Recent studies have shown that inhibition of *CDK4/6* enhances immunogenic cell death, mediated by activation of p73 and expression of DR5 in a pathway independent of p53.
- We sought to characterize the impact of *CDK4/6* expression on mutational profile, TME, and clinical outcomes in patients with dMMR/MSI-H CRC stratified by *TP53* mutational status.

Methods

- Tumor profiling was performed for 13,942 samples by NextGen Sequencing on DNA (592-gene panel or WES) and RNA (WTS) at Caris Life Sciences (Phoenix, AZ).
- 932 of these specimens were dMMR/MSI-H.
- Cohorts were created based on top (Q4) and bottom (Q1) quartiles of *CDK4/6* RNA expression (transcripts per million) and further divided based on *TP53*mt. *TP53*wt includes WT, VUS and benign/likely benign mutations
- Chi-square, Fishers-exact, and Mann Whitney U tests were used to determine statistical significance and adjusted for multiple hypothesis testing by Benjamini-Hochberg ($q < 0.05$).
- Cell infiltration in the TME was estimated by quanTIseq.
- Insurance claims data was obtained to calculate ICI-survival using Kaplan-Meier estimates from the initiation of treatment to last contact.

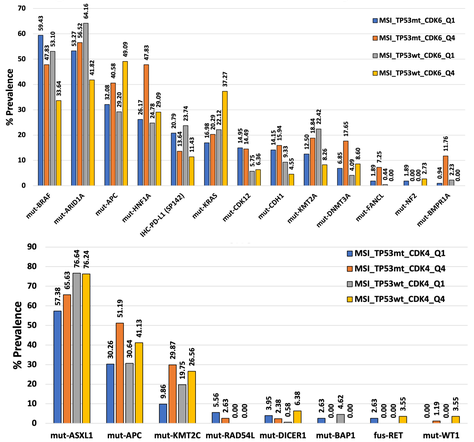
Results

Figure 1. *CDK4/6* Expression by Biopsy Site and Sidedness



CDK4 & *6* tumor expression levels were not significantly different in primary vs. metastatic sites, nor in left vs. right-sided tumors. *p<0.05

Figures 2 and 3. Co-Alterations by *TP53* status and *CDK4/6* Quartiles



CDK6-Q4 tumors were enriched for mutations in *APC*, *HNF1A*, *KRAS* and *DNMT3A*, while *CDK6*-Q1 was associated with *BRAF* mutations and *PDL1*+ tumors ($P < 0.05$). Mutations in *ARID1A*, *CDH1*, *KMT2A*, *FANCL*, *NF2* and *BMPR1A* showed opposite trends in *CDK6*-Q4 compared to Q1 depending on *TP53*mt. *CDK4*-Q4 tumors were enriched in *APC* and *KMT2C* mutations regardless of *TP53* mutation. In *TP53*wt, *ASXL1* mutations were similar in Q4 vs. Q1. Mutations in *DICER1* were enriched in *CDK4*-Q4 in *TP53*wt, but not *TP53*mt tumors.

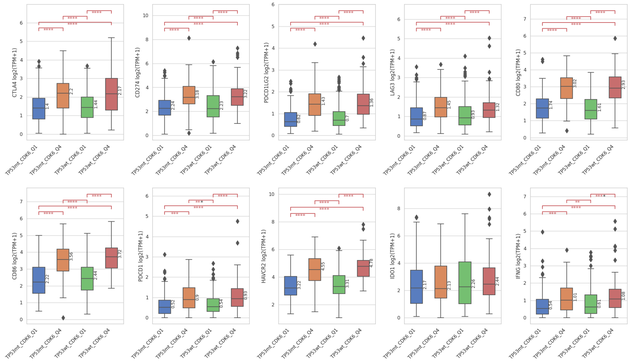
Table 1. Cohort Demographics and *TP53* expression by *CDK4/6* quartiles in MSI-H CRC

Cohort Characteristics	CDK4_Q1 (n=249)	CDK4_Q4 (n=225)	CDK6_Q1 (n=333)	CDK6_Q4 (n=179)
Median Age [range] (N)	70 [19 - >89] (249)	70 [18 - >89] (225)	71 [22 - >89] (333)	69 [18 - >89] (179)
Gender				
Female	61.0% (152/249)	56.4% (127/225)	60.1% (200/333)*	46.9% (84/179)*
Male	39.0% (97/249)	43.6% (98/225)	39.9% (133/333)*	53.1% (95/179)*
Tumor Sidedness				
Left	67.5% (168/249)	63.1% (142/225)	18.6% (62/333)	24.0% (43/179)
Right	18.1% (45/249)	24.9% (56/225)	68.2% (227/333)	60.3% (108/179)
Unclear	14.5% (36/249)	12.0% (27/225)	13.2% (44/333)	15.6% (28/179)
Biopsy Site				
Primary/Local	67.9% (169/249)	75.1% (169/225)	72.1% (240/333)	68.2% (122/179)
Metastatic	28.9% (72/249)	21.8% (49/225)	24.3% (81/333)	29.1% (52/179)
Unclear	3.2% (8/249)	3.1% (7/225)	3.6% (12/333)	2.8% (5/179)
TP53 status				
Wild-Type**	69.5% (173/249)	62.7% (141/225)	67.9% (226/333)	61.5% (110/179)
Mutated	30.5% (76/249)	37.3% (84/225)	32.1% (107/333)	38.5% (69/179)

* proportion of gender was significantly different between CDK6 Q1 vs Q4

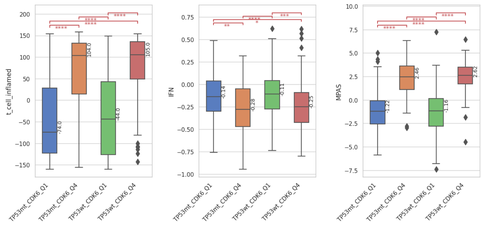
** WT includes *TP53*wt, VUS and benign/likely benign mutations

Figure 4. Association of Immune Checkpoint Gene Expression by *CDK6* quartiles



CDK6-Q4 tumors were associated with higher expression of immune checkpoint genes including *CTLA4, CD274, PDCD1LG12, LAG3, CD80, CD86, PDCD1, HAVCR2, IFNG* (fold change [FC] Q4 vs Q1: 1.65-3.23, $q < 0.05$, independent of *TP53*mt.

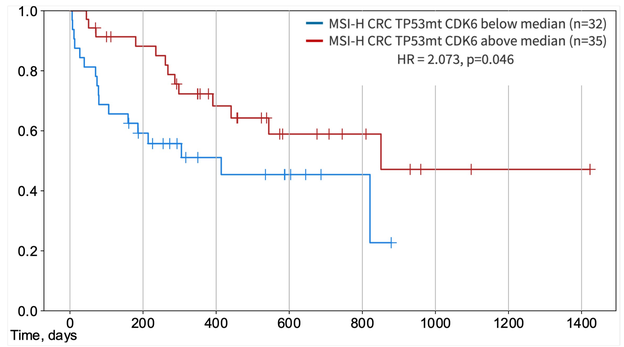
Figure 5. Association of Gene Signatures with *CDK6* Expression Stratified by *TP53* Mutation



The T-cell inflamed and MPAS signature scores were higher in *CDK6*-Q4 vs Q1 ($q < 0.05$), but showed an inverse trend in IFN. Similar results were observed for *CDK4* expression [data not shown].

*q<0.05, **q<0.01, ***q<0.001, ****q<0.0001

Figure 6. Association of *CDK6* Expression with Survival on ICI



In patients with *TP53*mt tumors, *CDK6* expression below the median was associated with shorter ICI survival (HR = 2.073, 95% CI 0.999-4.302, $P = 0.046$), whereas no difference was observed when patients were not stratified by *TP53* mutation.

CONCLUSIONS

dMMR/MSI-H CRC has distinct mutational profiles according to *TP53*mt status, and differential expression of immune-related genes and TME cell infiltration independent of *TP53* mutation in *CDK4/6* high vs low.

In our series, *CDK6* expression correlated with ICI treatment benefit in *TP53*mt tumors, warranting further studies to explore the potential of targeting the CDK4/6 axis to enhance ICI efficacy in MSI-H CRC.

References

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