PLK1 expression and KRAS mutations in colorectal cancer (CRC)

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Background

- Polo-like Kinase 1 (PLK1) is a serine/threonine protein kinase that has emerged as a next generation anti-angiogenic target in cancer therapy, with several PLK inhibitors in development.

- PLK1 is highly expressed in many cancers and is associated with poor prognosis.

- Oncogenic mutations in the TP53 protein KRAS are prevalent (35-40%) in colorectal cancer (CRC) and are associated with resistance to targeted therapies.

- KRAS-mutant (MT) cells are particularly dependent on genes implicated in mitotic functions, such as PLK1.

Objectives

- Evaluate gene expression levels of PLK1 in KRAS-MT versus KRAS-WT colorectal cancer.

- Determine if PLK1 expression is associated with DNA mutations, activated pathways and clinical characteristics in CRC.

Hypothesis/Goal:

- Inhibition of PLK1 expression could reverse the drug resistance of cancer cells and increase sensitivity to radiotherapy and chemotherapy even in drug-resistant mutant KRAS cancers.

- A better understanding of whether PLK1 is overexpressed in KRAS-MT versus WT colorectal cancers, and whether this is associated with other molecular and genetic features or clinical outcomes will help in determining its role as a therapeutic target.

- A Phase II trial to inhibit mutant MCR3 in second line combination with FOLFIri and bevacizumab (n=300/414) is not required.

- Preclinical data suggest syntocinon with mitotic and bevacizumab

Methods

- We retrospectively reviewed 4551 CRC tumors profiled with Caris Life Sciences from 2019 to 2020.

- Profiling included whole transcriptome sequencing, targeted next-generation sequencing, tumor mutational burden (TMB), deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) status, and immunohistochemistry.

- The Microenvironment Cell Populations (MCP)counter method was used to measure immune infiltration the tumor microenvironment.

- Median PLK1 expression was similar in KRAS-MT vs KRAS-WT tumors (28.6 vs 32.3 TPM; p=0.043).

- Tumors had significantly higher PLK1 expression compared to primary tumors (28.6 vs 32.3 TPM; p=0.001).

- Tumors in the top quartile (Q4) PLK1 expression group were more frequently associated with a rectal primary site compared to the bottom quartile (Q1) group (27.3% vs 17.7%; p=0.001).

- CRAs had increased mutation rates of TP53 (18.3% vs 66.5%), APC (78.7% vs 66.5%), and MSH6 (44.0% vs 13%) compared to Q1 (p<0.001). dMMR/MSI-H (8.6% vs 7.2%) and TMB (8.8% vs 2.9%) were significantly increased in Q4 compared to Q1 (p<0.001). Relative immune cell population and checkpoint gene expression increased gradually from Q1 to Q4 (p<0.001).

Primary Objectives:

- Evaluate gene expression levels of PLK1 in KRAS-MT versus KRAS-WT colorectal cancer.

- Determine if PLK1 expression is associated with DNA mutations, activated pathways and clinical characteristics in CRC.

Conclusions

- A lack of increased PLK1 expression suggests similar potential for PLK1 inhibitors in KRAS-MT tumors compared to KRAS-WT.

- Among PLK1 expression groups, proportionate increases in dMMR/MSI-H, TMB, and other immune-related markers suggested a potential response to immunotherapy with a PLK1 inhibitor in tumors with increased PLK1 expression.

- Combining immunotherapy with a PLK1 inhibitor might be a synergistic approach to increase sensitivity to PLK1-expressing CRC regardless of KRAS status.

References


